The long and the short of memory

Neuropsychological studies on the interaction of working memory and long-term memory formation

Bonnie van Geldorp

DONDERS
series

The long and the short of memory

Neuropsychological studies on the interaction of working memory and long-term memory formation

Bonnie van Geldorp

This research was supported by the Netherlands Organization for Scientific Research (NWO), grant number 452-08-005.

Netherlands Organisation for Scientific Research

ISBN
978-94-91027-86-4

Cover and lay-out design
Promotie In Zicht, Arnhem, The Netherlands

Print
Ipskamp Drukkers, Enschede, The Netherlands

The long and the short of memory

Neuropsychological studies on the interaction of working memory and long-term memory formation

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. mr. S.C.J.J. Kortmann,
volgens besluit van het college van decanen
in het openbaar te verdedigen op vrijdag 25 april 2014
om 12.30 uur precies

door

Bonnie van Geldorp
Geboren op 30 mei 1986
te Limmen

Promotor

Prof. dr. R.P.C. Kessels

Manuscriptcommissie

Prof. dr. I. Tendolkar *(University Duisburg-Essen, DE)*
Dr. M. Meeter *(Vrije Universiteit, Amsterdam)*
Prof. dr. J.I.M. Egger

Contents

Chapter 1 General Introduction

Memory is one of our key cognitive functions. We all experience some trouble with memory from time to time. Most often though, these problems do not affect our daily lives to a major extent. However, for many patients with brain disorders and diseases, memory problems can be very disabling. Many aspects of memory and its representation in the brain have been extensively researched in the past decades, but some issues remain topics of discussion. One of these debated issues is the role of the medial temporal lobe in working memory, which is the main focus of this thesis. Specifically, I will focus on the function of the medial temporal lobe in working memory and its interaction with long-term memory.

In the following paragraphs, I will first introduce the concepts of working memory and long-term memory and subsequently highlight which brain regions are known to be involved in both types of memory. Next, I will focus on the interaction between working memory and long-term memory, and the role of the medial temporal lobe in this. Finally, I will describe different theories concerning the role of the medial temporal lobe in working memory tasks and give an outline of the studies covered in the following chapters.

Working memory

In neuropsychology, working memory is generally accepted to represent a limited capacity store for actively maintaining information over a short period of time (that is, seconds) and for performing mental operations on this information (Gazzaniga, Ivry, & Mangun, 2002). Working memory is distinct from short-term memory in that it not only maintains information, but also manipulates it. Different models of working memory have been developed over the years. The two models that are most influential are the multi-store model by Baddeley and the embedded-process model by Cowan. Both models are described below.

Baddeley's multi-store model

Initially, the model by Baddeley and Hitch (1974) contained three major components: two slave systems and one coordinating system (see Figure 1). The visuospatial sketchpad is a limited-capacity store for visual information. The phonological loop is the verbal equivalent of the visuospatial sketchpad and retains and stores phonological input (i.e. information that can be articulated) for a few seconds by subvocally rehearsing the information (Baddeley, 1981).

The third component of the working memory model is the central executive, which supervises the two slave systems. In the initial model, the central executive was thought to perform all functions not explained by the slave systems (Baddeley

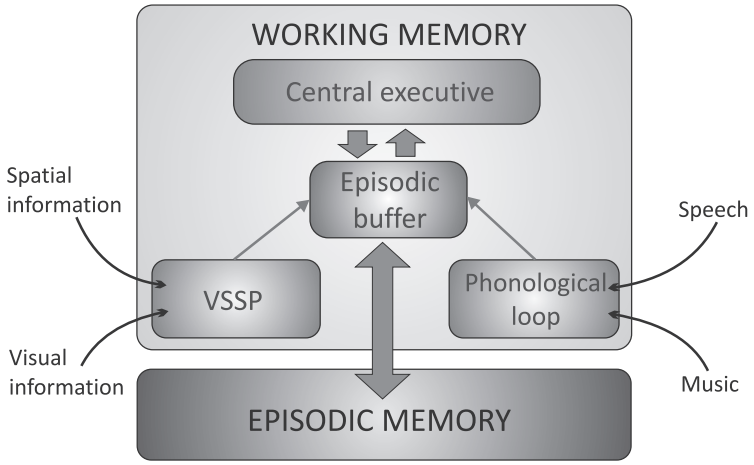

Figure 1 The working memory model by Baddeley (adapted from Kessels & Kopelman, 2012)

& Hitch, 1974). Some have even argued that the central executive was nothing more than an homunculus – a "little man" making all important decisions (Parkin, 1998). The central executive is now defined as manipulating control processes and attentional resources (Baddeley, 1981, 2003). It allows performing dual tasks by dividing attention and it allows inhibition of habitual or automatic responses (Baddeley, 1996). Another function of the central executive is to focus on one stream of information while discarding the other – a function referred to as selective attention (Baddeley, 1996). These functions are part of what in the neuropsychological literature is referred to as executive function, associated with prefrontal lobe function (Shallice & Burgess, 1991).

In order to solve multiple problems with his initial working memory model (for example the fact that there is no store for integrated pieces of information), Baddeley added a fourth component to the model: the episodic buffer (Baddeley, 2000). It is a limited-capacity store in which information is bound together into integrated episodes (Baddeley, 2003). It also serves as an interacting system between working memory and long-term memory. In the present thesis, the experiments are focused on the binding of different features into working memory. Within Baddeley's model, the main focus of my research is on the episodic buffer.

Cowan's embedded-process model

The embedded-process model by Cowan comprises three components: long-term memory, currently activated memory and the focus of attention (Cowan, 1999, see Figure 2). The model is called 'embedded' because the focus of attention is a subset of activated memory and active memory is a subset of long-term memory. It is assumed that working memory requires activation and awareness, but also long-term memory knowledge.

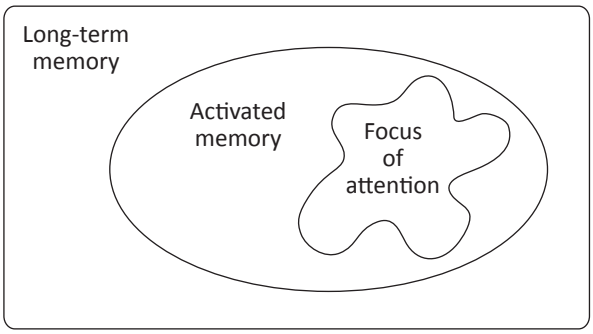

Figure 2 The working memory model by Cowan (adapted from Cowan, 1999)

Like Baddeley, Cowan states that working memory has limits. Memory remains activated for about 10 to 20 seconds before it starts to fade (Cowan, 1999). In order to remain active, the information within active memory has to be reactivated, for example by rehearsing. The focus of attention is limited in capacity, in that it can contain about 3 to 5 items or chunks at the same time. In short, active memory is time-limited and the focus of attention is capacity-limited. In contrast, long-term memory is unlimited in capacity (Cowan, 1999).

In cognitive activities, we use the available resources. This means that we try to hold all information necessary within the focus of attention. When the capacity of the focus of attention is exceeded, the excess of information can be kept in active memory. If it is not possible to keep all required information active, long-term memory information can be accessed.

In comparison to Baddeley's model, Cowan's model is more unitary in nature. Activated memory comprises all activation across sensory modalities or activation in any form of representation. Cowan's model does not rely on specialized buffers, which means that temporary storage (i.e., activated memory) occurs in the same brain regions that support its perceptual representation (Cowan, 1999).

Long-term memory

Definition of long-term memory

Already in 1890, long-term memory was put forward as a distinct memory system by William James. He called it secondary memory and defined it as the vast body of knowledge stored over lifetime (James, 1890). After that, long-term memory has been defined as a fairly permanent store for information (Atkinson & Shiffrin, 1968), or a vast store of knowledge and a record of prior events (Cowan, 2008).

Obviously, long-term memory contains many different kinds of information. Several subtypes of long-term memory have been defined (see Figure 3). Declarative memory incorporates all knowledge that we have conscious access to. Non-declarative memory is unconscious to memory and contains for example memory for motor skills. Declarative memory is subdivided into episodic memory (memory for events in our lives) and semantic memory (general knowledge without any recollection of the specific event in which this knowledge was acquired). In this thesis, I will focus specifically on episodic memory, the declarative long-term memory system that enables us to encode and store new information and retrieve it at a later point in time.

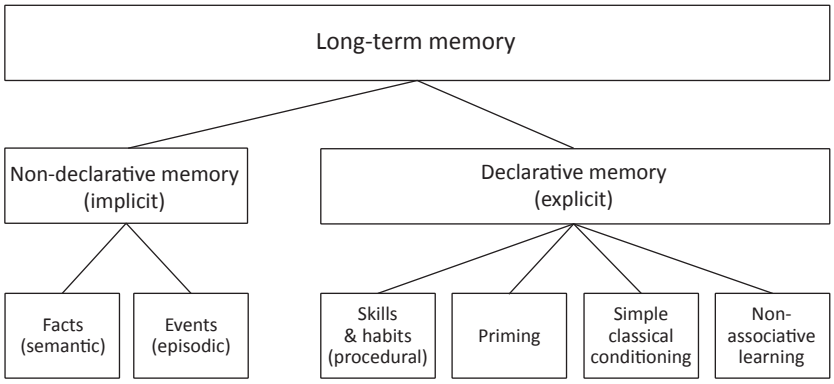

Figure 3 Long-term memory and its subsystems (adapted from Squire, 2004)

Paradigms in episodic memory research

There are different ways to examine episodic memory. In a free-recall paradigm, memory is tested without any cues. Generally, this means that the participant is asked an open question and he or she has to actively retrieve the information from memory, such as a word-list learning paradigm. In a cued-recall or recognition

paradigm, the participant is presented with a sensory cue that may aid in retrieving the memory trace. The cue can trigger a sense of familiarity by activating part of the memory trace. Here, I used only recognition paradigms, because of the large amount of to-be-remembered information and the complexity of the material and also to induce optimal performance in brain-diseased patients.

The cognitive neuroscience of memory

Brain regions involved in working memory

The brain regions that are involved in working memory vary widely, depending for example on specific task requirements and stimulus material. It has been shown that maintenance of information is mediated by persistent activity of the same cortical regions that process the incoming information (D'Esposito, 2007). Therefore, which areas are involved in maintaining the information depends on the type of material, for example its modality (whether it is visual or verbal).

However, sensory areas are not the only areas involved in working memory; supramodal regions such as the prefrontal cortex and parietal cortex are also involved (Linden, 2007). The area that has most consistently been associated with working memory is the prefrontal cortex. Early single-cell recording studies in monkeys showed that neurons in the prefrontal cortex fired persistently during the retention interval of tasks that required the monkey to maintain information over a short period of time (Funahashi, Bruce, & Goldman-Rakic, 1989; Fuster & Alexander, 1971; Kubota & Niki, 1971). Recent neuroimaging studies support the finding that the prefrontal cortex is activated during the retention interval of working memory tasks (e.g. Curtis & D'Esposito, 2003). In sum, the prefrontal cortex is considered important for maintaining information in working memory. In addition, the prefrontal cortex is also involved in higher-order processes needed for working memory by means of interactions with sensory areas (D'Esposito, 2007). That is, the prefrontal cortex contains the goals of your behavior and the rules for achieving these goals (Miller & Cohen, 2001). It can bias sensory systems and responses by using top-down signals to enhance relevant and suppress irrelevant stimuli (D'Esposito, 2007; Miller & Cohen, 2001).

Finally, parietal regions are involved in working memory. The prefrontal cortex interacts with posterior regions of the brain (Linden, 2007), in order to control and integrate representations. Mainly, these regions provide the attentional resources required to perform the task, limiting working memory capacity (Linden, 2007). In addition, posterior parietal areas are involved in active search processes (Linden, 2007).

In sum, working memory not only requires sensory areas to process and maintain the incoming information, it also requires a fronto-parietal network. In addition, the hippocampus and related medial temporal lobe areas are also found to be involved in specific working memory tasks, as will be described in more detail below.

Brain regions involved in episodic memory

Perhaps the most famous patient in memory research is H.M., described by (1957). In 1953, he underwent surgery because his severe seizures were unresponsive to medication. Approximately 8 cm of his medial temporal lobe was resected on both sides of the brain. After surgery, his seizures were less incapacitating than before. Strikingly though, he presented with severe memory loss. He had complete anterograde amnesia (i.e., he was unable to form any new memories after surgery) and partial retrograde amnesia (remembering no events from the three years preceding his surgery). This severe memory deficit was in sheer contrast to his intact intellectual ability.

Importantly, his immediate memory and motor skill learning seemed intact. As long as he could continuously rehearse the numbers, he could retain three-digit numbers for as long as 15 minutes (Squire, 2009b). In addition, H.M. could be trained in visuomotor skill tasks: tracing the outline of a five-pointed star, while only being able to see his hand and the star as reflected in a mirror. He acquired this skill over several training sessions, although he could not recall any of these sessions (Squire, 2009b). This case led to the distinction between several memory systems: declarative memory (including immediate memory and long-term memory) and procedural memory (e.g. motor skill learning and habit learning). It also led the authors to conclude that there is a clear relationship between the removal of the hippocampal complex (and related structures) and declarative memory impairment (Scoville & Milner, 1957).

Accumulating research in both patients and animals has led to the term "medial temporal lobe memory system" (Squire & Zola-Morgan, 1991), which includes the hippocampus and the adjacent perirhinal, entorhinal, and parahippocampal cortices. These adjacent cortices provide the major route by which information from the neocortex reaches the hippocampus. The hippocampus then binds together the relevant cortical sites that represent the memory for an event (Squire, Stark, & Clark, 2004; Squire & Zola-Morgan, 1991). For a lengthy period after learning, the system continues to be involved by reorganizing and consolidating the information. In time, memories become independent of the medial temporal lobe memory system and are stored in distributed neocortical structures (Squire et al., 2004, 2004; Squire & Zola-Morgan, 1991). According to the multiple trace theory of memory, this is only the case for semantic memory; the

medial temporal lobe continues to be involved in the storage and retrieval of episodic memories (Nadel, Samsonovich, Ryan, & Moscovitch, 2000). For a review on different theories concerning the consolidation of memories (including the multiple trace theory), see Meeter and Murre (2004). The medial temporal lobe is not only involved in the storage of memories, but also in the retrieval of recent or remote memories (Maguire, 2001). Many studies confirmed the critical role of medial temporal lobe structures in episodic memory (for reviews, see for example Maguire, 2001; Squire et al., 2004; Squire, 2004).

As is the case with most cognitive functions, there is more than one area involved in episodic memory. Many studies have examined the role of the prefrontal cortex in the formation of episodic memory (for a review, see Blumenfeld & Ranganath, 2007). As stated before, the prefrontal cortex has been known for its important role in cognitive control (Miller & Cohen, 2001). Patients with prefrontal damage experience memory problems, especially when controlled selection of goal-relevant information is required during encoding or retrieval (Blumenfeld & Ranganath, 2007). Neuroimaging studies showed that prefrontal regions support memory formation by means of goal-related processes of selection and inhibition (depending on the ventrolateral prefrontal cortex; Blumenfeld, Parks, Yonelinas, & Ranganath, 2011), as well as organizational processes, control processes, and the encoding of relational information (depending on the dorsolateral prefrontal cortex; Blumenfeld et al., 2011; Blumenfeld & Ranganath, 2006, 2007).

Finally, parietal regions are also related to episodic memory (Schoo et al., 2011; Wagner, Shannon, Kahn, & Buckner, 2005). At least one patient study shows that patients with parietal lesions experience problems with episodic memory retrieval (Davidson et al., 2008). For a recent review on the role of the posterior parietal cortex in episodic memory, see Schoo et al. (2011). They state that amongst others, the parietal cortex subserves attentional processes, similar to its role in working memory. The superior parietal cortex is found to be involved in top-down processes that support retrieval search, monitoring and verification (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008).

In summary, several categories of brain regions are implicated in episodic memory formation and retrieval: areas processing the information at hand (depending on the type of stimuli); areas related to attentional processes (parietal areas) and control processes (frontal areas) constituting a fronto-parietal network; and areas related to storage (medial temporal lobe and specifically the hippocampus). This is roughly in line with what Kim (2011) proposed in his review.

The interaction between working memory and episodic memory

Following the literature described above, it is now clear that working memory primarily involves prefrontal cortical areas, whereas episodic memory primarily involves the medial temporal lobe. Although the double dissociation suggests that working memory and episodic memory are independent systems (Squire, 2004), overlapping brain regions are involved in several types of memory. However, working memory and episodic memory are typically investigated separately. When both were investigated within the same study, the formats of the working memory and episodic memory tasks were very dissimilar, and hence, hardly comparable.

The role of the medial temporal lobe in working memory and episodic memory

In the past decade, an increasing number of studies have investigated the role of the medial temporal lobe in working memory tasks. Imaging studies have shown that the hippocampus and related structures within the medial temporal lobe are activated during working memory tasks, specifically when the task involves a relational aspect (Hannula & Ranganath, 2008; D. Luck et al., 2010; Mitchell, Johnson, Raye, & D Esposito, 2000; Piekema, Kessels, Mars, Petersson, & Fernández, 2006; Piekema, Kessels, Rijpkema, & Fernández, 2009; Piekema, Rijpkema, Fernández, & Kessels, 2010). In all of those tasks, features or items had to be associated; a process called binding. For example, Mitchell et al. (2000) found hippocampal activity when participants had to retain objects together with their location. It can therefore be argued that the medial temporal lobe is also involved in working memory processing.

Results from patient studies led to the same conclusion. Patients with medial temporal lobe damage (and amnesia) were found to be impaired in various working memory binding tasks. For example, amnesic patients with bilateral damage to the hippocampus or related medial temporal lobe structures were found to be impaired in associating items to scenes, faces to scenes, and objects to locations (Hannula, Tranel, & Cohen, 2006; Jeneson, Mauldin, & Squire, 2010; Olson, Page, Moore, Chatterjee, & Verfaellie, 2006). Patients with Alzheimer's disease showed deficits in object-color binding (Della Sala, Parra, Fabi, Luzzi, & Abrahams, 2012; Parra, Abrahams, Fabi, et al., 2009) and patients with right-sided hippocampal lesions showed deficits in color-location binding (Braun et al., 2011).

From these studies, it may be concluded that the medial temporal lobe is not only involved in episodic memory, but also in specific working memory tasks. Other studies suggest that the medial temporal lobe is involved in the long-term consolidation of associative information (Kersten & Earles, 2010; Prince, Daselaar,

& Cabeza, 2005; Qin et al., 2009; Shing, Werkle-Bergner, Li, & Lindenberger, 2008). Taken together, the abovementioned studies led to the idea that the medial temporal lobe is involved in associative processes in general. However, there are more explanations possible as to why the medial temporal lobe appears to play a role in specific working memory tasks.

Why is the medial temporal lobe involved in working memory tasks?

First, as described above, medial temporal lobe involvement during working memory tasks may reflect its role in associative processes. The relational memory theory states that the medial temporal lobe is important for relational memory in general, irrespective of whether the information is to be remembered for the short term or the long term (Cohen et al., 1999; Eichenbaum, Otto, & Cohen, 1994; Konkel & Cohen, 2009). Others have supported this notion or put forward similar ideas (see for example Henke, Buck, Weber, & Wieser, 1997; Henke, 2010; Shing et al., 2008; Silver, Goodman, & Bilker, 2012).

Another explanation that has been put forward is that the involvement of the medial temporal lobe in working memory actually represents incidental long-term memory encoding (Ezzyat & Olson, 2008; Ranganath, Cohen, & Brozinsky, 2005). In fact, medial temporal lobe activity during working memory tasks is found to be related to subsequent long-term memory formation (Bergmann, Rijpkema, Fernández, & Kessels, 2012; Schon, Hasselmo, Lopresti, Tricarico, & Stern, 2004). Longer delays may also induce more long-term encoding processes. A finding in line with this notion is that longer delays result in deficits in patients with MTL damage (Buffalo, Reber, & Squire, 1998; Shrager, Levy, Hopkins, & Squire, 2008).
Finally, there is a theory that states that the medial temporal lobe is involved in working memory tasks only when working memory capacity is exceeded (Jeneson, Mauldin, Hopkins, & Squire, 2011; Jeneson et al., 2010; Jeneson & Squire, 2012). Working memory is limited in its capacity, so when working memory capacity is exceeded, long-term memory processes may be needed to support performance on the task. For example, when the memory load is high or when the delay is long, the medial temporal lobe gets involved. Binding processes may also require more resources than working memory can handle, explaining why patients with medial temporal lobe damage fail on working memory binding tasks. This theory is in line with Cowan's embedded process model (Cowan, 1999), because it also states that long-term memory is involved when short of other resources.

In summary, (at least) three possible explanations can be postulated as to why the medial temporal lobe is involved in working memory binding tasks. That is, it could be due to the relational aspect of the tasks and, hence, truly related to actual working memory processing. It could also be due to incidental long-term memory encoding processes, and/or due to an overload of working memory capacity.

Outline: participants and studies

So far, I have outlined the main research questions of my thesis: how do working memory and long-term memory interact, and why is the medial temporal lobe involved in working memory tasks? In order to address these questions, I examined several patient populations in the studies described in the following chapters.

In the study described in **chapter two**, I examined patients with early Alzheimer's disease using a spatial working memory binding task. The Box Task required participants to search for objects in boxes and maintain the object-location bindings. In addition to this working memory paradigm, subsequent episodic memory was examined upon completion of the working memory task, by asking the participants to relocate the objects to the locations in which they were previously found.

In **chapter three**, I describe a study in stroke patients. These patients suffered damage to various parts of the brain, but not the medial temporal lobe. This enables us to examine working memory binding when the medial temporal lobe is not damaged. Participants' performance was examined for three conditions: working memory for objects, for locations and for object-location bindings. Note that we contrast single features with bound information in this study, in order to gain more insight in the theory that specifically associative information requires medial temporal lobe involvement.

Since working memory related hippocampal activity has been associated with spatial processing (Crane & Milner, 2005; M. L. Smith & Milner, 1981), I then performed a series of studies also using non-spatial stimuli. In **chapter four**, we examined patients with specific lesions to the medial temporal lobe. Patients with unilateral anterior temporal lobectomy (but no amnesia) participated in a working memory binding task in which object-location binding was contrasted with other types of binding. The question is whether a difference in performance can be found between relational binding (binding separate entities; i.e. object-object binding and object-location binding) and conjunctive binding (binding features of an object; i.e., object-color binding).

Chapter five describes a study in which I used a similar paradigm to examine patients with extensive anterograde amnesia due to their brain damage; that is, patients with Korsakoff's syndrome. In these patients, the diencephalic-hippocampal system is lesioned. In addition to working memory binding, we also examined subsequent episodic memory. By means of a varying delay length during working memory, I also tried to shed some light on the idea of long-term encoding processes that may take place during working memory binding tasks as a function of delay length.

In **chapter six**, I describe the exact same paradigm used in a different patient population. Since the lesions of patients with Korsakoff's syndrome are not limited to the medial temporal lobe and are often the result of chronic alcohol abuse, this study focused on a group of patients in which the lesions are relatively limited to the medial temporal lobe (especially in the early stages of the disease): patients with Mild Cognitive Impairment and Alzheimer's dementia. In addition to the role of the medial temporal lobe in working memory binding and subsequent episodic memory performance, I also looked at the effect of age by comparing three different age groups of healthy participants.

Chapter seven describes a different approach to measuring working memory binding performance. In this study, the precision with which participants could remember the orientation of colored bars was used as a measure of working memory performance. Patients with Mild Cognitive Impairment or Alzheimer's dementia performed a task in which they had to maintain the orientation of colored bars. Using this task, I tried to investigate whether the medial temporal lobe is involved in working memory binding because of its role in relational memory, or because working memory capacity is exceeded.

In **chapter eight**, I contrasted conjunctive binding and relational binding in three different age groups. Object and color were used in both conditions, ensuring the use of non-spatial features. In addition, we examined the effect of an interfering task on the two types of binding, in order to examine whether diminished resources affect working memory binding.

Finally, in **chapter nine**, I summarize all studies in this thesis, discuss what we have learned from these studies, highlighting the clinical relevance, discuss what issues remain open to discussion and which studies could be done in the future to resolve these issues.

Chapter 2 Associative working memory and subsequent episodic memory in Alzheimer's disease

Published as:
Van Geldorp, B., Konings, E.P.C., Van Tilborg, I.A.D.A., Kessels, R.P.C. Associative working memory and subsequent episodic memory in Alzheimer's disease. Neuroreport. 23(2):119-123, January 25, 2012. doi: 10.1097/WNR.0b013e32834ee461.

Abstract

Recent studies indicate deficits in associative working memory in medial-temporal lobe amnesia patients. However, it is unclear whether these deficits reflect working memory processing or are due to hippocampally mediated long-term memory impairment. We investigated associative working memory in relation to subsequent episodic memory formation in patients with early Alzheimer's disease to examine whether these findings reflect deficits in long-term encoding rather than 'pure' working memory processing. Nineteen Alzheimer's disease patients and 21 controls performed a working memory task in which objects had to be searched at different locations. The subsequent episodic memory test required participants to reposition objects to their original locations. Alzheimer's disease patients were impaired on associative working memory and subsequent episodic memory, but they performed above chance at high-load episodic memory trials. This suggests that when working memory capacity is exceeded, long-term memory compensates.

Introduction

Deficits in episodic memory due to medial temporal lobe atrophy are a key characteristic of Alzheimer's disease, which includes the dementia phase of the disease as well as its prodromal stage mild cognitive impairment (Albert et al., 2011; McKhann et al., 2011). However, it is less clear if and to what extent working memory is affected. Standard neuropsychological working-memory tests (e.g., span tasks) generally reveal no deficits in Alzheimer patients (Guarch, Marcos, Salamero, Gasto, & Blesa, 2008; Kramer et al., 2006). Conversely, patients with working memory deficits seem to perform well on at least some long-term memory tasks (Shallice & Warrington, 1970). This double dissociation has led to the notion that memory can be divided into separate systems, in which working memory is predominantly supported by the prefrontal cortex and long-term memory by the medial temporal lobe (Squire, 2009a).

In contrast to this dissociation, recent studies demonstrated medial temporal lobe activation during working memory tasks (Nichols, Kao, Verfaellie, & Gabrieli, 2006a; Schon et al., 2004), in particular when participants have to associate multiple items or features (Olson et al., 2006; Piekema et al., 2009, 2010). In addition, studies have shown that early Alzheimer's disease patients are impaired on working memory tasks that require object-colour binding, colour-colour binding or object-location binding (Kessels, Meulenbroek, Fernández, & Olde Rikkert, 2010; Parra, Abrahams, Fabi, et al., 2009; Parra et al., 2011). This suggests that the medial temporal lobe is not only involved in long-term memory function, but also in working memory and that working memory and long-term memory may not function totally independent of one another (Ranganath & Blumenfeld, 2005).

From a theoretical point of view, Baddeley's working memory model is relevant (Baddeley, 2007). It contains auditory and visuospatial slave systems and a supervisory module, the central executive. Later, the episodic buffer was added to the model. It integrates information from various sources (i.e. binding) and transfers information into long-term memory (Baddeley, 2007). In addition, the episodic buffer serves as an "overflow buffer", providing extra storage capacity when the capacity of the slave systems is exceeded. It could therefore be argued that the medial temporal lobe involvement observed during associative working memory tasks reflects functions of the episodic buffer. Alternatively, medial temporal lobe involvement may simply reflect long-term encoding processes, since medial temporal lobe activation during working memory maintenance is found to predict subsequent episodic memory performance (Nichols et al., 2006a; Schon et al., 2004). It was the aim of our study to investigate this explanation.

As deficits in working memory for spatial associations have already been demonstrated in early Alzheimer's disease patients in the mild cognitive impairment

stage (Kessels et al., 2010), the current study extends the literature by including patients in the dementia phase and by extending the paradigm with a subsequent memory test. Concerning the subsequent memory task, we hypothesize a general deficit in Alzheimer's disease patients compared to controls. More importantly, by directly comparing associative working memory performance with subsequent episodic memory for the same stimuli, we are able to examine whether any long-term encoding has taken place during the working memory task as this should be reflected in above-chance performance on the subsequent memory task.

To our knowledge, no studies have directly compared associative working memory and subsequent episodic memory formation in Alzheimer's disease. In addition, investigating associative working memory may lead to a better understanding of the development of episodic memory deficits, as it has been suggested that episodic memory problems may result from difficulties in binding information into complex memories (Mayes, MacDonald, Donlan, Pears, & Meudell, 1992; Naveh-Benjamin, 2000). Furthermore, this setup may have clinical implications as well, as patients with early Alzheimer's disease show working memory problems that currently often remain undetected by standard neuropsychological tests.

Methods

Nineteen patients diagnosed with (amnestic or multiple-domain) mild cognitive impairment (n=12) (Albert et al., 2011) or dementia (n=7) (McKhann et al., 2011) due to Alzheimer's disease were recruited from Geriatrics and Neurology departments of the Elkerliek Hospital, Helmond, the Netherlands (8 males; mean age 75.3, SD=7.4; mode educational level classified using 7 categories 5, range 3-7). Mean score on the Mini-Mental State Examination, a brief screening for cognitive impairment (Lezak, 2004), was 23.7, range 17-29. Performance on the Digit Span working-memory subtest of the Wechsler Adult Intelligence Scale – Third Edition (Lezak, 2004) was 11.35, SD=2.27. Diagnoses were supported by neuroimaging, neuropsychological testing and clinical interview. General exclusion criteria were a history of any neurological or psychiatric disease (unrelated to Alzheimer's disease).

Twenty-one community-dwelling, high-functioning healthy volunteers were examined (8 males; mean age 72.7 years, SD 7.1 years; modus educational level 5, range 3-7) and were matched on age ($F(1,18)=1.28$, $p=.27$), sex (Mann-Whitney $U=191.5$, $p=.83$) and education (Mann-Whitney $U=198.5$, $p=.98$). Exclusion criteria for the controls were subjective memory complaints and a history of neurological or psychiatric disease. All participants had normal or corrected-to-normal vision.

The study was approved by the hospital's Institutional Review Board; all participants fulfilled the criteria for competence and provided written informed consent.

Working memory paradigm

All participants completed a computerized visuospatial working memory task (Box Task (van Asselen, Kessels, Wester, & Postma, 2005), see Figure 1), in which pictures of closed boxes (1 by 1 cm) are presented at various locations within a 19 by 19-cm frame on a 15" touch-sensitive monitor. Participants were instructed to search through the boxes to find a hidden target object by 'opening' the boxes. When a target was found, a new target object was presented that had to be searched. Participants were instructed that a previously found object remained hidden in its box. Thus, participants not only had to remember which boxes were recently searched, but also which boxes contained previous targets. When all target objects were found, a new trial with a new spatial layout and an increased number of boxes started. The task included one practice trial containing 3 boxes and four trials containing 3, 4, 6, and 8 boxes respectively. There was no time limit, but participants were motivated to respond within reasonable time (i.e. within a few seconds).

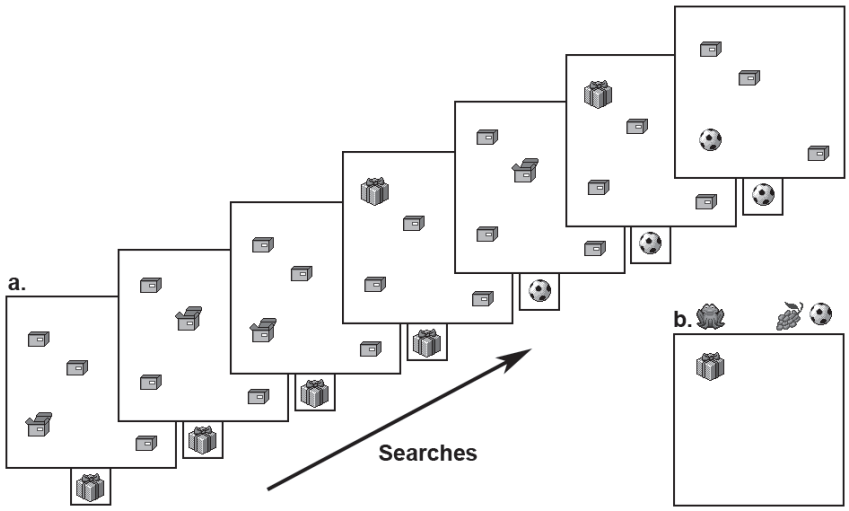

Figure 1 **a**. Schematic overview of the working memory paradigm. The participant has to search for the target object. A within-search error is made when the participant returns to a box that was already found to be empty in that search. Such an error is displayed in the third panel. The sixth panel shows a between-search error: the participant opens a box that already contained an object from a previous search. **b**. Schematic overview of one trial of the subsequent episodic memory task.

Three error measures are computed (see Fig. 1a). First, *within-search errors* are made by returning to a box that was already opened within that search. This measurement reflects the ability to keep track of locations recently visited and is therefore assumed to reflect visuospatial sketchpad functioning (Baddeley, 2007). Second, *between-search errors* are made by returning to a box that already contained a target from a previous search. This measurement reflects the ability to maintain object-location information for longer periods of time. Hence, the ability to avoid between-search errors is assumed to rely on the episodic buffer (Kessels et al., 2010). Third, the *strategy score* measures search efficiency by counting how often a participant starts a search with a different box. Since following a predetermined search sequence would be more efficient, a low strategy score indicates an efficient search strategy (Owen, Downes, Sahakian, Polkey, & Robbins, 1990).

Subsequent episodic memory task

After an unfilled delay of approximately five minutes, participants performed an unexpected delayed cued-recall test, developed using Object Relocation software (Kessels, Postma, & de Haan, 1999). In this task, participants had to place objects back to the locations where they were presented during the working memory task (see Figure 1b). All objects were presented in random order above an empty square and could be placed at any location within that square. This task included one practice trial containing 3 objects, and four trials containing 3, 4, 6, and 8 objects respectively. Self-corrections were allowed and again, no time limit was set.

Here, we measured the absolute distance in millimetres between the original location of an object and the location where the participant relocated that specific object. The absolute error is the total of these distances for all objects in a display (Kessels et al., 1999).

Analyses

A doubly multivariate 2 (Group: controls vs. patients) x 4 (Set size: 3, 4, 6, 8) repeated measures ANOVA, with within-search errors, between-search errors and strategy score as dependent variables was used to analyse the data from the working memory paradigm. Mauchly's test showed that the assumption of sphericity was violated, which is why the degrees of freedom were corrected according to the Greenhouse-Geisser estimate. For the subsequent memory task, a multivariate 2 (Group: controls vs. patients) x 4 (Set size: 3, 4, 6, 8) repeated measures ANOVA, with absolute error as dependent variable was used.

An alpha of .05 was used in all analyses. For all effects, effect sizes were calculated (η_p^2), which describe the proportion of variance explained by the factor in question. To check whether both groups performed above chance, ten healthy students were asked to perform only the subsequent episodic memory task. Here,

participants were instructed to place objects at the "correct" location by guessing the most appropriate location, i.e. without having seen the original displays in the working memory paradigm. As none of these participants had any knowledge of the original locations of the objects, their performance was used as an estimate of chance performance (Kessels, Postma, Wester, & de Haan, 2000).

Results

Working memory paradigm

Patients made more within-search errors than controls ($F(1,39)=5.54$, $p=.02$, $\eta_p^2=.12$; see Figure 2). In addition, a main effect of set size was found, with more errors being made with increasing set size ($F(1.90,73.93)=5.40$, $p<.01$, $\eta_p^2=.12$). The interaction effect of set size and group was marginally significant ($F(1.90,73.93)=2.69$, $p=.08$, $\eta_p^2=.07$), indicating that an increasing set size led to a greater increase in errors for patients than for controls.

With respect to between-search errors, patients made more errors than controls ($F(1,39)=11.32$, $p<.01$, $\eta_p^2=.23$), see Figure 2b. More between-search errors were made in trials with a larger set size ($F(1.71,66.65)=67.32$, $p<.001$, $\eta_p^2=.63$) and an increasing set size led to a greater increase in errors for patients than for controls ($F(1.71,66.65)=5.99$, $p=.006$, $\eta_p^2=.13$).

Analysis of the strategy score showed a main effect of set size ($F(2.45,95.53)=219.94$, $p<.001$, $\eta_p^2=.85$), indicating that larger set sizes lead to a higher strategy score. No group difference was found for strategy ($F(1,39)=1.65$, $p=.21$).

Subsequent episodic memory task

Patients presented with a significantly larger absolute error than controls, reflecting a worse performance (see Fig. 2c; $F(1,39)=5.81$, $p=.02$, $\eta_p^2=.13$). In addition, larger set sizes resulted in larger absolute error scores ($F(6,34)=55.20$, $p<.001$, $\eta_p^2=.91$). Pair-wise comparisons showed that controls performed significantly above chance level ($t(29)=-3.49$, $p<.01$). For the patients, a trend towards above-chance performance was observed ($t(27)=-1.95$, $p=.06$). Further analyses showed that patients performed significantly above chance level when trials had either 3 ($t(26.35)=-3.05$, $p<.01$) or 8 boxes ($t(27)=-2.45$, $p=.02$), but not for the conditions with 4 and 6 boxes ($p=.92$ and $p=1$, respectively).

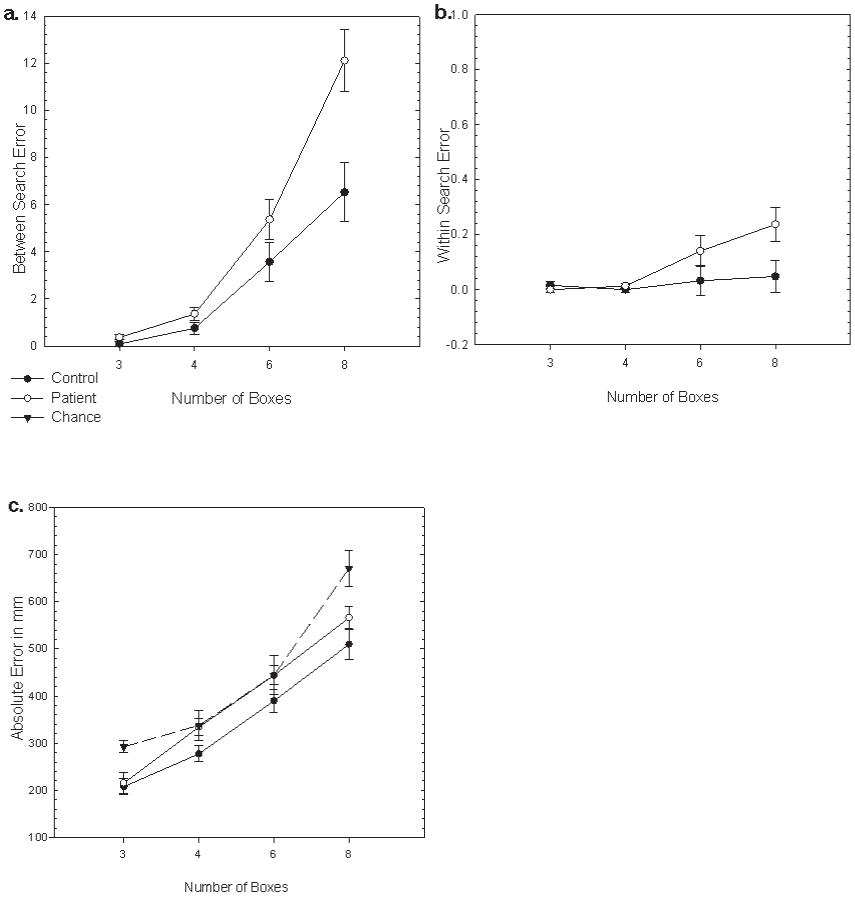

Figure 2 Results for the working memory paradigm (panel a and b) and the subsequent episodic memory task (panel c), for the increasing number of boxes in Alzheimer's disease patients and controls. **a**. Number of Between-search errors. **b.** Within-search errors. **c.** Absolute error. Higher scores represent worse performance.

Discussion

The present study shows that patients with early Alzheimer's disease demonstrate clear deficits on an associative working memory task. Although subsequent episodic memory formation was found to be severely impaired, patients performed above chance on trials with either a low (3 boxes) or high memory load (8 boxes). The above-chance level performance on the 3-box condition suggests that this

condition is too easy. In the 8-box condition, this above-chance performance may indicate that the episodic buffer was successfully recruited during high-load working memory trials, which will be discussed in more detail below. These findings confirm the notion that Alzheimer patients do not only have long-term memory deficits, but also deficits in working memory tasks that rely on the integration of information. Often this remains undetected by standard neuropsychological tests. Indeed, Digit Span performance was unimpaired in these patients. To our knowledge this is the first study to assess both associative working memory and subsequent long-term memory formation with a similar task paradigm using the same stimuli. Compared to a previous study by Kessels et al. (2010) that examined the same working memory paradigm in mild cognitive impairment patients (without the subsequent episodic memory test), more within-search errors and between search errors were present in the current study. Although absolute differences are small, this may be the result of including patients who are already in the dementia stage of the disease and thus perform worse than patients in the mild cognitive impairment stage. Although it was not our aim to make specific claims about neural representations, previous studies have established that medial temporal lobe atrophy typically accompanies early Alzheimer's disease (van der Flier & Scheltens, 2009). Our findings are in agreement with recent evidence showing that the medial temporal lobe plays an important role in associative working memory (Olson et al., 2006; Piekema et al., 2009).

It remains to be clarified whether these associative working memory deficits in Alzheimer's disease are limited to object-location associations. That is, it could be argued that spatial features rather than the binding process itself led to hippocampal involvement. However, previous results have shown binding problems with non-spatial features as well. For example, short-term memory for object-colour associations is compromised in patients with Alzheimer's dementia (Parra, Abrahams, Fabi, et al., 2009; Parra et al., 2011).

Our results can be interpreted in view of Baddeley's working memory model, specifically its episodic buffer (Baddeley, 2007). Patients with early Alzheimer's disease have problems keeping track of recently visited locations in the working memory task, which may point to a deficit in the visuospatial sketchpad. No group differences were found for strategy usage. This finding is in line with previous studies (Kessels et al., 2010; van Asselen et al., 2005) and indicates that executive functions are relatively spared in early Alzheimer's disease. Since binding is a function of the episodic buffer, the impairment in associating objects and locations in working memory may be due to impaired functioning of the episodic buffer.

In addition, the overflow function of the episodic buffer may elucidate why an increasing working memory load affected patients more than controls. It may also explain why patients performed above chance level on subsequent episodic

memory trials with 8 boxes. In trials with fewer boxes, processing at the visuospatial sketchpad level may suffice, but when working memory capacity is exceeded, the episodic buffer may be recruited as an overflow buffer. As the episodic buffer is the interface between working memory and long-term memory (Baddeley, 2007), additional involvement of the episodic buffer may have resulted in activation of the Alzheimer's disease patients' residual long-term encoding processes. This, in turn, may explain the improved subsequent memory on the 8-box condition. Although the underlying mechanisms of this episodic buffer deficit are still under debate, impairments in working memory binding may underlie deficits in episodic memory formation, both of which rely on the medial temporal lobe (Ranganath & Blumenfeld, 2005).

Conclusion

In summary, episodic buffer dysfunction may result in associative working memory deficits in patients with early Alzheimer's disease. As associative working memory is especially impaired when memory load is high, the overflow function of the episodic buffer may be involved. This additional involvement may have resulted in some transfer of the information into long-term memory, which explains the better long-term memory performance for the high-load trial.

Chapter 3 Single-item and associative working memory in stroke patients

Published as:
Van Geldorp, B., Kessels, R.P.C., Hendriks, M.P.H. Single-item and associative working memory in stroke patients. Behavioural Neurology. 26 (3): 199-201, 2013. Doi: 10.3233/BEN-2012-129010.

Abstract

In this study, we examined working memory performance of stroke patients. A previous study assessing amnesia patients found deficits on an associative working memory task, although standard neuropsychological working memory tests did not detect any deficits. We now examine whether this may be the case for stoke patients as well. The current task contained three conditions: one spatial condition, one object condition and one binding condition in which both object and location had to be remembered. In addition, subsequent long-term memory was assessed. The results indicate that our sample of stroke patients shows a working memory deficit, but only on the single-feature conditions. The binding condition was more difficult than both single-feature conditions, but patients performed equally well as compared to matched healthy controls. No deficits were found on the subsequent long-term memory task. These results suggest that associative working memory may be mediated by structures of the medial temporal lobe.

Introduction

Stroke may affect any area of the brain resulting in a variety of cognitive deficits (Jaillard, Naegele, Trabucco-Miguel, LeBas, & Hommel, 2009). Identifying the profile of cognitive deficits is relevant for rehabilitation purposes for individual patients. In clinical practice, standard neuropsychological tests are used to determine working-memory deficits in patients. Typically, span-like tasks such as digit span or Corsi block tapping task are used. However, these working memory tests do not involve an associative (or binding) component. This is relevant because deficits on an associative working-memory task were found in amnesia patients who showed no deficits on the WAIS-III digit span (Van Geldorp, Bergmann, Robertson, Wester, & Kessels, 2012). Here, we investigate whether an associative working memory task is sensitive in stroke patients as well. Also, a subsequent memory task was administered to investigate the role of long-term encoding in relation to working memory.

Methods

Participants

In the present study, 24 stroke patients (mean age: 52.08, SD=11.15, mode education level: 5, range 2-7, 18 males) and 31 matched controls (mean age: 50.65, SD=13.99, mode education level: 5, range 2-7, 15 males) were included. All patients were recruited from the rehabilitation center Groot Klimmendaal in Arnhem, the Netherlands. The patients had all experienced an ischaemic or hemorrhagic stroke (10 left-sided, 12 right-sided and 2 bilateral). All participants provided written informed consent. The groups were matched with respect to age, gender distribution and education (all p>.10). Working memory performance, as measured with the WAIS-III digit span, did not significantly differ between patients (mean performance: 13.67, SD=3.10) and controls (mean: 13.72, SD=3.92; F<1).

Experimental Task

All participants completed a computerized delayed-match-to-sample task for working memory (see figure 1a; Sternberg, 1966), with three blocks of 18 trials each, resulting in a total of 54 trials. In each trial, three stimuli are presented at different locations within a 5-by-5-grid for 1000 ms each. All locations on the grid are used, except for the center location. A delay period of 3 seconds follows, in which the participant has to remember the object, location or both.

In the case of the object condition, the probe is presented as an object in the centre of the grid. The participant then has to decide whether or not it is a match

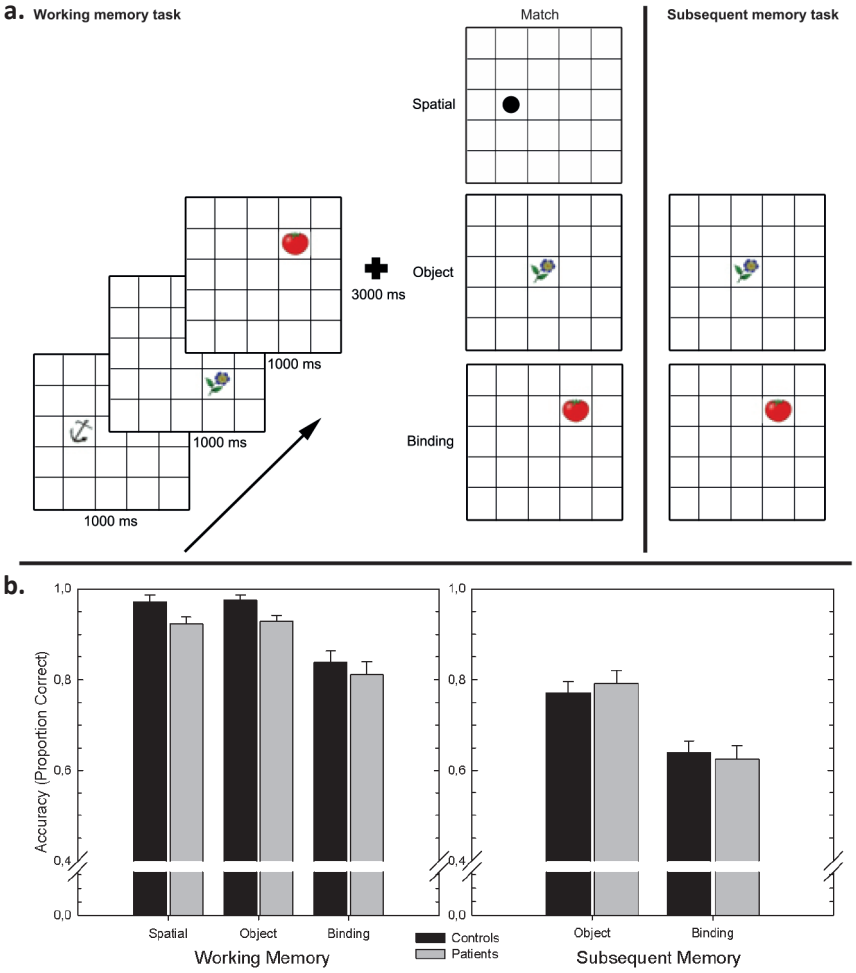

Figure 1 **a.** Schematic overview of the experiment. Three stimuli are presented for 1000 ms each. After a delay period of 3000 ms, a probe is presented. Here, matching probes are shown for the three different conditions (spatial, object and binding). For the binding condition, a non-matching probe is a recombination of an object and a location presented in that trial. In the subsequent memory task, long-term memory for objects and bindings is assessed. **b.** Results for the working memory task and the subsequent memory task.

to the stimuli presented in that trial. In the case of the spatial condition, the probe is a black dot at a specific location and in the case of the binding condition it is an object at a specific location. In the latter case, the non-matching probe is a

combination of a stimulus and a location from that trial, in order to minimize familiarity-based responses.

Approximately five minutes after completing this working memory task, a subsequent memory task was performed, consisting of two blocks of 12 trials each, to assess episodic memory for both objects and object-location associations. As all locations were used multiple times, we could not assess episodic memory for locations.

Results

The results are displayed in Figure 1b. All participants performed significantly above chance level (all $p<.01$). For the working memory task, a repeated measures ANOVA with condition (object, spatial and binding) as within-subject factor and group (patient or control) as between-subject factor was performed. Since Mauchly's test showed that the assumption of sphericity was violated, we corrected the degrees of freedom, using the Greenhouse-Geisser correction.

The results show a significant effect of task condition ($F(1.59, 84.56)=36.37$, $p<.001$), with performance on the binding condition being worse than on both the object condition ($p<.001$) and spatial condition ($p<.001$). No differences were found between the object and spatial condition. In addition, a significant group effect was observed ($F(1,53)=4.38$, $p=.04$). This effect seems to be largely caused by a group difference in both the spatial ($p=.05$) and object condition ($p=.02$). No group difference was observed in the binding condition ($p=.48$). There was no significant interaction effect of group by condition ($F<1$).

The results of the subsequent memory task also show a significant effect of condition ($F(1,53)=29.27$, $p<.001$), but no significant group or interaction effect ($F<1$). When comparing the working memory task with the subsequent memory task, we observed a significant difference between tasks ($F(1,53)=172.34$, $p<.001$), but no significant interaction effect of group by task ($F(1,53)=2.12$, $p=.15$). This means that the memory performance decline that can be observed in the subsequent memory task is equal for both groups.

Discussion

The present study clearly indicates that although our sample of stroke patients in the chronic stage did not show working-memory deficits on a standard neuropsychological test, they clearly had deficits on an experimental working-memory task. However, it is interesting that the impairment lies in the single-feature

conditions and not in the associative condition. These results extend previous findings showing that associative working memory may be mediated by structures of the medial temporal lobe (Bergmann et al., 2012). This notion is further supported by our results showing that the groups performed equally on the subsequent long-term memory task, which relies on medial temporal-lobe function (Bergmann et al., 2012). On the other hand, memory for single features may predominantly be subserved by the fronto-parietal working-memory network (Rottschy et al., 2012), a brain region that is more susceptible to stroke than the medial temporal lobe.

It could be argued that the associative condition has a higher memory load and may thus be more challenging than the single-feature conditions, but this appears to be equally the case for patients and controls. Also, no binding deficit was found in the patients, in contrast to the single-feature conditions. In a future study, the working memory load could be systematically varied to investigate the role of memory load. In addition, it was not possible to relate the lesion location to the pattern of impairment in our sample, but future studies should investigate the neuroanatomical substrate of single-feature vs. associative working memory in more detail.

Acknowledgements

We thank Maaike Gaastra en Maartje Hutten for their assistance in collecting the data.

Chapter 4 Different types of working memory binding in epilepsy patients with unilateral anterior temporal lobectomy

Published as:
Van Geldorp, B., Bouman, Z., Hendriks, M.P.H., Kessels, R.P.C. Different types of working memory binding in epilepsy patients with unilateral anterior temporal lobectomy. Brain and Cognition. 85: 231-238, 2014. DOI: 10.1016/j.bandc.2013.12.009.

Abstract

The medial temporal lobe is an important structure for long-term memory formation, but its role in working memory is less clear. Recent studies have shown hippocampal involvement during working memory tasks requiring binding of information. It is yet unclear whether this is limited to tasks containing spatial features. The present study contrasted three binding conditions and one single-item condition in patients with unilateral anterior temporal lobectomy.

A group of 43 patients with temporal lobectomy (23 left; 20 right) and 20 matched controls were examined with a working memory task assessing spatial relational binding (object-location), non-spatial relational binding (object-object), conjunctive binding (object-colour) and working memory for single items. We varied the delay period (3 or 6 s), as there is evidence showing that delay length may modulate working memory performance.

The results indicate that performance was worse for patients than for controls in both relational binding conditions, whereas patients were unimpaired in conjunctive binding. Single-item memory was found to be marginally impaired, due to a deficit on long-delay trials only.

In conclusion, working memory binding deficits are found in patients with unilateral anterior temporal lobectomy. The role of the medial temporal lobe in working memory is not limited to tasks containing spatial features. Rather, it seems to be involved in relational binding, but not in conjunctive binding. The medial temporal lobe gets involved when working memory capacity does not suffice, for example when relations have to be maintained or when the delay period is long.

Introduction

It is well established that the medial temporal lobe, specifically the hippocampus, is essential for long-term memory formation and retrieval (Squire, 2009a). However, it is less clear if and how the medial temporal lobe is involved in working memory (WM) processes. It is generally assumed that WM and long-term memory are distinct memory systems, since double dissociations have been described in patients with severely impaired WM, but intact long-term memory and vice versa (Scoville & Milner, 1957; Shallice & Warrington, 1970; E. K. Warrington & Weiskrantz, 1970). These memory systems have their own neural correlates, with long-term memory being represented in the medial temporal lobe and WM being represented in a fronto-parietal network (Curtis, 2006; Shallice & Warrington, 1970; Squire, 2009a; E. K. Warrington & Weiskrantz, 1970).

More recently, results from both patient and neuroimaging studies have led to some discussion concerning this strict distinction of memory systems (for a review, see Ranganath & Blumenfeld, 2005). For example, a lesion study by Olson et al. (2006) presented evidence for medial temporal lobe involvement in a WM task. Participants had to actively maintain three objects, locations or object-location associations over short delays (i.e., 1 s or 8 s). Patients with bilateral lesions of the medial temporal lobe performed significantly worse than controls in maintaining object-location associations. In addition, neuroimaging studies documented hippocampal activity when participants were actively maintaining object-location associations (D. Luck et al., 2010; Mitchell, Johnson, Raye, & D'Esposito, 2000; Piekema et al., 2006).

So far, most WM binding studies focused on object-location binding. Although Olson et al. (2006) did not find a location-only deficit, it could be argued that the spatial character of the task, rather than associative processes per se, contribute to medial temporal lobe involvement. There is increasing evidence that medial temporal lobe involvement during WM tasks is not only material-specific (e.g. spatial vs non-spatial) but also depends on the type of binding (Parra et al., 2011; Piekema et al., 2010). Therefore, we included non-spatial conditions. We designed a WM task based on the studies by Olson et al. (2006) and Mitchell et al. (2000) to examine whether the medial temporal lobe is involved in WM binding in general, or in specific types of binding only.

There are several ways to distinguish different types of binding. Here, we use the same taxonomy as used in Parra et al. (2009) who distinguish *conjunctive* binding and *relational* binding. Conjunctive binding refers to the association between objects and their features, which results in a blended representation of features. Associating an object and its colour is an example of conjunctive binding. Another term for conjunctive binding would be unitized binding (Cohen, Poldrack,

& Eichenbaum, 1997; Eichenbaum et al., 1994). Relational binding refers to the association between different individual features or items. For example, we refer to relational binding when associating an object with another object or with its location.

To our knowledge, only one patient study systematically compared different types of WM binding (Braun et al., 2011). They found that patients with right hippocampal lesions performed normally on two types of conjunctive binding (colour-shape and colour-letter binding), but were impaired in spatial relational binding (in this case colour-location binding). This may suggest that the medial temporal lobe is involved only in relational binding and not in conjunctive binding. However, an alternative explanation may be that spatial components drive this effect, which may even be attenuated as only patients with lesions in the right hippocampus were included (Milner, Johnsrude, & Crane, 1997).

Our task compares four conditions: conjunctive binding (object-colour binding), spatial relational binding (object-location binding), non-spatial relational binding (object-object binding), and single items. The task was performed by a group of patients who had undergone a neurosurgical treatment for their intractable temporal lobe seizures. The major advantage of these patients is that they all have selective lesions to the anterior temporal lobe. That means that any deficits observed can be attributed to this neural region with more certainty than when patients with other etiologies (like Alzheimer's disease, where more global lesions are found) are concerned. However, it could also be argued that a history of long-lasting epilepsy can result in a functional reorganisation of the neural substrates underlying memory functions (Braun et al., 2008; S. S. Spencer, 2002). We included both patients with left and patients with right-sided lesions, making it possible to evaluate possible lateralization effects.

With respect to relational binding, we expect patients to show impaired performance on spatial relational binding, in line with the studies described above (Braun et al., 2011; Mitchell, Johnson, Raye, & D'Esposito, 2000; Olson et al., 2006). Non-spatial relational binding was assessed using house-face associations, as an fMRI study demonstrated that house-face associations activated the medial temporal lobe (Piekema et al., 2009, 2010). Based on these fMRI results, we expect that patients will also show impaired performance on this type of binding.

Concerning the role of the medial temporal lobe in conjunctive binding, mixed results have been found. Previous studies found no evidence for hippocampal involvement during object-colour binding (Braun et al., 2011; Piekema et al., 2006, 2010). Associating an object with its colour may be a low-level perceptual process achieved earlier in the visual stream, demanding little resources (Piekema et al., 2006, 2010; Rossi-Arnaud, Pieroni, & Baddeley, 2006). In addition, Cohen and colleagues showed that blended or unitized representations of features, as opposed

to non-unitized relational bindings, can be created by structures outside the hippocampus (Cohen et al., 1997; Eichenbaum et al., 1994). Conversely, one study demonstrated deficits in object-colour binding in patients with Alzheimer's disease, who also have profound hippocampal dysfunction (Parra, Abrahams, Fabi, et al., 2009).

Finally, in addition to the three binding conditions, a single-item condition was included. Based on previous studies, patient performance was expected to be unimpaired in this condition (Braun et al., 2011; Olson et al., 2006; Parra, Abrahams, Fabi, et al., 2009; Piekema et al., 2006). In contrast, some studies have found deficits in WM for single items. For example, studies in amnesic patients have demonstrated WM deficits for single items for delay periods longer than 6 seconds (Buffalo et al., 1998; Nichols, Kao, Verfaellie, & Gabrieli, 2006b). A long delay length may cause an overload of WM capacity, which then results in long-term encoding processes that may activate the medial temporal lobe (Jeneson & Squire, 2012; Jeneson, Wixted, Hopkins, & Squire, 2012). For these reasons we varied delay periods in all conditions (3 or 6 s).

In summary, this study investigates WM for single items and three types of binding in patients who underwent an anterior temporal lobectomy. We examine the hypothesis that only relational binding involves the medial temporal lobe. This means that patients are expected to show unimpaired performance on the single-item condition as well as the conjunctive (object-colour) binding condition. In contrast, patients are expected to show deficits in both types of relational binding, that is spatial (object-location binding) and non-spatial (object-object binding) relational binding. In line with previous studies, we may also expect an effect of delay, in that patient performance would be worse for items and conjunctions maintained for longer delay periods (i.e. 6 seconds).

Materials and Methods

Participants

A total of 43 patients and 20 controls were tested. Data from one patient and one control were excluded from further analyses, because they performed more than two standard deviations below the group average. All data from the remaining 42 patients and 19 controls were included in the analyses. All patients (37 right-handed and 5 left-handed) were recruited from Epilepsy Centre Kempenhaeghe, the Netherlands and had undergone a neurosurgical treatment for their intractable temporal lobe seizures. All resections include unilateral removal of 3-6 cm of anterior temporal neocortex along with the amygdalohippocampal formation. Patients were divided into two groups according to the lateralization of the lesion:

22 patients with a left temporal lobectomy (MTL-L) and 20 patients with a right temporal lobectomy (MTL-R).

Table 1 Participant characteristics and performance on standard neuropsychological tests

	MTL-L group	MTL –R group	Controls	Statistic, *p*
N	22	20	19	
Age (Mean, SD)	42.5 (10.1)	45.7 (12.3)	46.84 (10.4)	F (2,58)=0.7, n.s.
Sex (M/F)	17/5	9/11	7/12	χ^2 (2)=7.7, p=.02*
Education level (Modus, range)	6 (3-6)	4 (3-7)	5 (3-6)	χ^2 (2)=1.0, n.s.
NART IQ (Mean, SD)	95.0 (13.4)	95.0 (10.2)	99.58 (11.5)	F<1, n.s.
Seizure free (Yes/No)	17/5	19/1	.	χ^2 (1)=2.7, n.s.
Anti-Epileptic drugs (No/Mono/Poly)	2/4/16	1/8/11	.	χ^2 (2)=2.5, n.s.
Seizure onset age (Mean, SD)	14.8 (10.2)	23.4 (16.5)	.	F (1,39)=4.2, p=.047*
Duration of epilepsy (Mean, SD)	26.1 (15.2)	18.6 (13.7)	.	F (1,39)=2.8, n.s.
Neuropsychological tests[a] (Mean, SD)				
WAIS-III Working Memory Index	101.1 (18.0)	90.9 (32.2)	103.0 (17.9)	F (2,45)=1.2, n.s.
Digit Span	10.1 (3.8)	10.3 (3.3)	11.2 (3.4)	F<1, n.s.
Arithmetic	10.5 (3.3)	9.1 (2.9)	10.2 (2.8)	F<1, n.s.
Letter-Number Sequencing	10.1 (3.4)	9.8 (4.3)	10.4 (3.5)	F<1, n.s.
WMS-R Delayed Memory Index	96.0 (17.1)	101.2 (18.5)	.	F<1, n.s.

Note. Education level was recorded using seven categories from Verhage (1964). Intelligence was measured using the Dutch version of the National Adult Reading Test (NART; Nelson, 1982; Schmand, Bakker, Saan, & Louman, 1991). Working memory was assessed by the Working Memory Index of the Wechsler Adult Intelligence Scale-third edition (WAIS-III; D. Wechsler, 1997).

[a] Standardized scores (mean=10, SD=3). Neuropsychological test data were not for all patients available. Data for the WAIS-III was available for 15 MTL-L patients and 14 MTL-R patients and data for the WMS-R was available for 20 MTL-L patients and 19 MTL-R patients.

* Significant < .05.

The control group included 18 right-handed and 1 left-handed healthy volunteers, on average matched for age and education level (assessed using the seven categories from Verhage 1964) with the patient group. None of the participants had a history of psychiatric or neurologic disease other than epilepsy or reported current substance abuse (including alcohol). All participants had normal or corrected-to-normal vision. The study was approved by the Institutional Review Board of Epilepsy Centre Kempenhaeghe and all participants provided written informed consent. Participant characteristics and performance on standard neuropsychological tests are summarized in table 1.

Experimental task

The WM paradigm (see figure 1) is a delayed-match-to-sample task (Sternberg, 1966), based on previous studies (Mitchell, Johnson, Raye, & D'Esposito, 2000; Olson et al., 2006). The design was adapted from Piekema et al. (2010) and included one single-item condition and three binding conditions: 1) spatial relational binding: object-location binding; 2) non-spatial relational binding: object-object binding; 3) conjunctive binding: object-colour binding.

The task consisted of 18 trials for each condition randomly presented in 4 blocks, resulting in a total of 72 trials. In each trial, three trial-unique house-face combinations were randomly presented for 2500 ms each. Faces were pictures of males and houses were pictures of modern-day detached homes. Stimuli were randomly presented in 6 different colours on 24 possible locations in a 5 5 grid with a blank centre box. During one trial, all stimuli presented had different colours and locations.

Trials for each of the four conditions were randomly interleaved. A cue presented at the start of each trial informed participants which stimulus or combination of stimuli/features had to be retained. This means that although each trial contained the same type and amount of information, participants had to retain a different subset of this information, depending on the condition cued. This was deliberately designed in such a way, so that all conditions had an equal memory load. That is, participants were required to encode and maintain 6 items or features in each trial. When participants were cued that a single item or house-face combination would be probed, they had to maintain all six stimuli. For conjunctive binding and spatial relational binding, the cue indicated whether features had to be maintained for either the faces or the houses. This means that participants had to maintain three stimuli with their accompanying three features (either colour or location).

Keeping the memory load equal also means that some of the information presented was irrelevant in order to perform optimally in that specific trail. Colour was only relevant for the conjunctive binding condition and location was

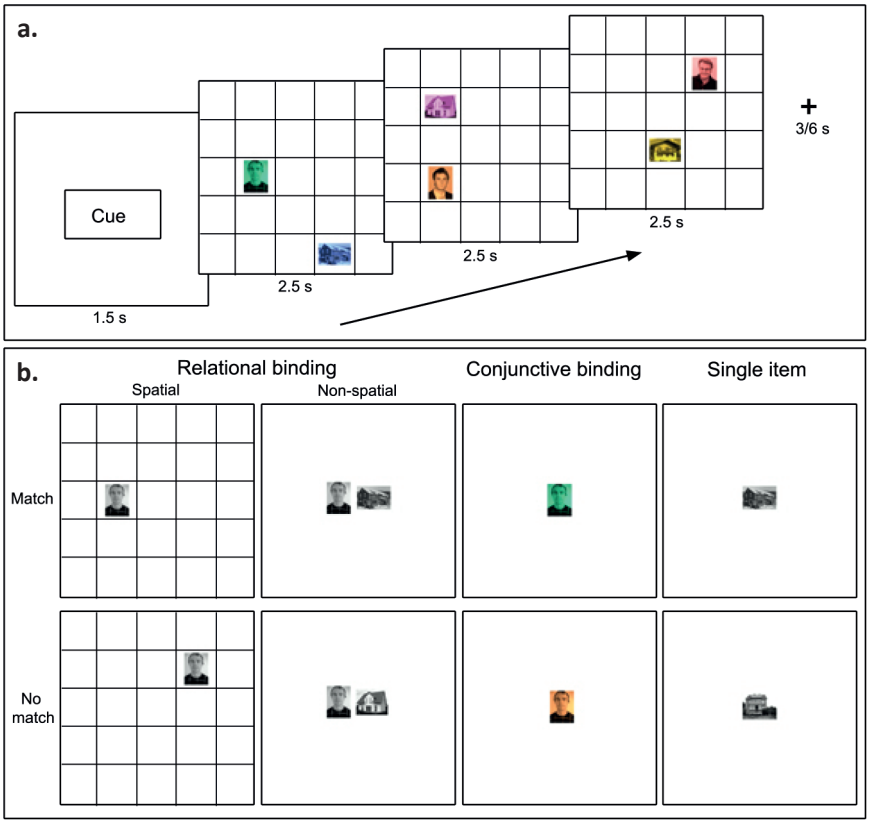

Figure 1 Schematic overview of the task. **a.** Stimulus phase. Three trial-unique house-face combinations were presented in six different colours, on a 5x5 grid. A cue preceding the stimuli indicated what information had to be retained. The delay was either 3 or 6 seconds. **b.** Probe phase. There are four conditions: two types of relational binding (spatial and non-spatial), conjunctive binding and a single-item condition. In all binding conditions, a non-matching probe consists of a rearranged pair of stimuli from the stimulus phase. In the single-item condition, either a house or a face was probed.

only relevant for the spatial relational binding condition. As stated before, in the conjunctive binding and spatial relational binding conditions, either the faces or the houses were irrelevant. Note that each condition contains the same amount of relevant and irrelevant features. To be specific, relevant to the single-item condition are the three faces and houses. Irrelevant are the six colours and six locations.

Relevant to the conjunctive binding condition are either three houses or three faces combined with three colours. Irrelevant are three faces or houses, their (three) colours and all six locations. Relevant to the spatial relational binding condition are either three houses or three faces combined with their three locations. Irrelevant are three faces or houses, their three locations and all six colours. Relevant to the non-spatial relational binding condition are three houses and three faces. Irrelevant are the six colours and six locations. In summary, trials for each condition contained six relevant features and twelve irrelevant features.
After an unfilled delay period of either 3 or 6 seconds a probe was presented. In the single-item condition the probe consisted of a grey-scaled face or house presented in the centre of the screen. For non-spatial relational binding, the probe consisted of a grey-scaled face and a grey-scaled house in the centre of the screen. For spatial relational binding, it consisted of a gray-scaled object presented at a certain location within the grid. Finally, for conjunctive binding, the probe was a coloured object in the centre of the screen. In the single-items condition, the probe could either be a repetition (match) of one of the stimuli presented, or a new stimulus (no match). In the binding conditions, probes were either a repetition (match) or a recombination (no match) of stimuli/features from that specific trial, in order to prevent familiarity-based responses. Participants were instructed to indicate by button press whether the probe presented belongs to the current stimulus set or not.

Analyses

The proportion of correct answers was measured. As each test probe has two optional responses, chance level performance would be a score of .50. An alpha of .05 is used in all analyses. Effect sizes (η_p^2) were computed that describe the proportion of variance explained by the factor in question, independent of the other variables.

First, we compared the patient groups using a 2 (group: MTL-L, MTL-R) x 4 (condition: single-item, conjunctive binding, spatial relational binding, non-spatial relational binding) × 2 (delay: short, long) repeated measures ANOVA. Since this analysis showed no effects of lateralization (main effect of group: $F(1,40)<1$, $p=.89$, $\eta_p^2<.001$), both groups were combined into one patient group in the following analyses in order to increase power.
Then, we performed a 2 (group: patients, controls) × 4 (condition: single-item, conjunctive binding, spatial relational binding, non-spatial relational binding) × 2 (delay: short, long) repeated measures ANOVA in order to examine the effects of delay and condition for patients and controls. Since the groups now differed in the number of participants, we examined whether the population variances were equal using Levene's test.

In order to examine our a priori hypotheses, we used an independent samples *t*-test. Patients were compared to controls for each condition, first combining short and long delays and then for both the short and long delays separately.

Results

The groups did not significantly differ with respect to age, education level and intelligence level (all $p>.10$). The patient groups (MTL-L vs. MTL-R) did not significantly differ with respect to absence of postsurgical seizures, epilepsy duration and use of anti-epileptic drugs (all $p>.10$). Small, yet significant differences were found for sex distribution ($p=.02$) and age at seizure onset ($F(1,39)=4.22$, $p=.047$). Post-hoc analyses revealed that the MTL-L group had more male than female participants, whereas this distribution was reversed in MTL-R and controls (MTL-L vs. MTL-R $p=.03$; MTL-L vs. controls $p=.01$). The MTL-R group had a later age of onset ($M=23.42$) as compared to the MTL-L group ($M=14.75$). However, these variables do not affect scores for the WM task as shown in multivariate ANOVAs (sex distribution: $F(8,52)=1.31$, $p=.26$ and age at seizure onset: $F(8,32)=0.32$, $p=.95$). Therefore, no covariates were included in the analyses. Consistent with findings from WM studies in patients with temporal lobe lesions (Cowey, 1996; Shin et al., 2009; Tudesco et al., 2010), WM performance, as measured by standard neuropsychological tests (i.e., the WAIS-III Working Memory Index (D. Wechsler, 1997), see Table 1), did not significantly differ between patients and controls (all $p>.30$).

Independent *t*-tests (test value: 0.50) revealed that both groups performed significantly above chance level (50%) in all conditions of the WM task (all $p<.002$). Mean scores are presented in figure 2 and 3.

The 2 × 4 × 2-repeated measures ANOVA revealed a main effect of group ($F(1,59)=5.40$, $p=.02$, $\eta_p^2=.08$), with patients performing significantly worse than control participants. In addition, a main effect of condition ($F(2.63, 155.13)= 11.70$, $p<.001$, $\eta_p^2=.17$) was observed. Bonferroni-corrected post-hoc analyses revealed worse performance on non-spatial relational binding relative to all other conditions (all $p<.002$). No interaction effects were found (all *p*-values>.05). Levene's test showed no significant differences in the homogeneity of variance for any of the conditions (all *p*-values>.1).

With respect to patients' performance in the different conditions, we had the a priori hypothesis that both relational binding conditions would show selective impairments. Patients performed significantly lower than controls on non-spatial relational binding ($t(59)=2.28$, $p=.03$, $d=.67$), marginally lower on spatial relational binding ($t(59)=1.89$, $p=.06$, $d=.53$) and on single-item maintenance ($t(59)=1.77$, $p=.08$, $d=.48$), but the groups did not differ on conjunctive binding ($t(59)=0.92$, $p=.36$, $d=.25$).

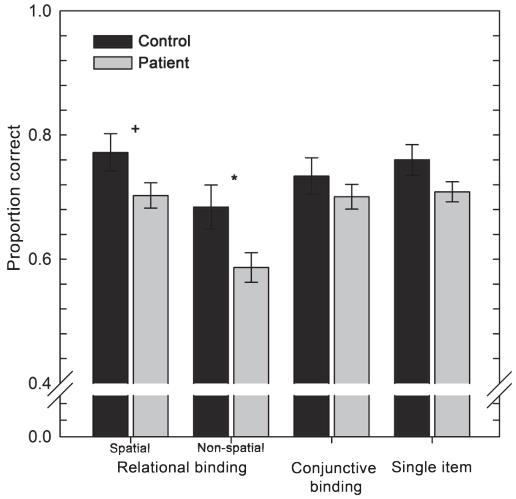

Figure 2 Mean scores and standard errors of proportion correct answers for patients and controls over both delay lengths, separated by condition.
* Significant (p<.05), + marginally significant.

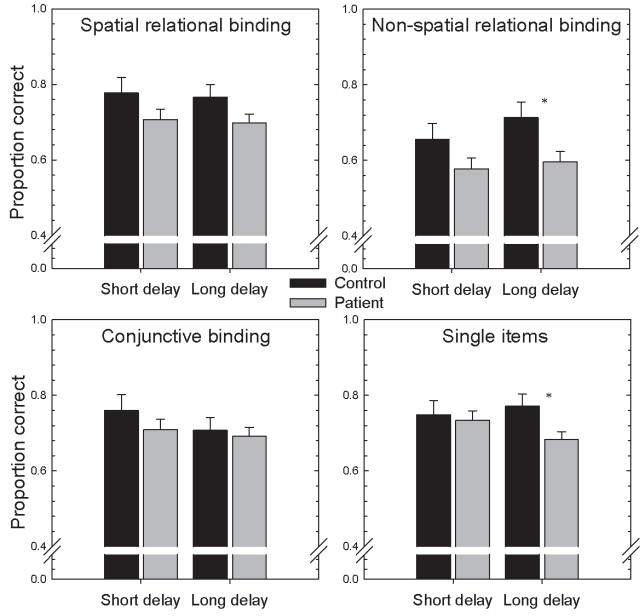

Figure 3 Mean scores and standard errors of proportion correct answers for patients and controls on all conditions.

No overall effect of delay was found (F<1), but our a priori hypothesis stated that patients would perform worse than controls on long delays in the single item or conjunctive binding conditions. The data revealed that patients performed significantly worse than controls when maintaining single items over long delays (t(59)=2.37, p=.02, d=.62), but showed no deficit when maintaining single items over short delays (t(59)=0.32, p=.75, d=.09). The same results were found for non-spatial relational associations: a deficit for long-delay trials (t(59)=2.39, p=.02, d=.69), but not for short-delay trials (t(59)=1.51, p=.14, d=.44). For spatial relational binding, there was neither a group difference for the short-delay trials (t(59)=1.43, p=.16, d=.41) nor for long-delay trials (t(59)=1.68, p=.10, d=.46). Likewise, the conjunctive binding condition showed no group difference for either the short (t(59)=1.02, p=.31, d=.27) or long delay (t(59)=0.38, p=.70, d=.11).

Discussion

The present study investigated different types of WM binding in patients with unilateral anterior temporal lobectomy as treatment of intractable temporal lobe seizures. Importantly, our patients were not densely amnesic (see also the scores within the normal range on the Delayed Memory Index from the WMS-R (D. Wechsler, 1987), table 1), which is why any effects that we find cannot be attributed to an overall memory problem. We expected patients to show deficits in relational binding, but not conjunctive binding. Relational binding is argued to rely on hippocampal functioning (Piekema et al., 2010), whereas conjunctive binding may rely on structures other than the hippocampus (Cohen et al., 1997; Eichenbaum et al., 1994; Parra et al., 2011; Piekema et al., 2006).

The results show that overall, patients performed worse than controls on the WM task. Although no significant group by condition interaction effect was found, we tested our a priori hypothesis, using planned comparisons and reported effect sizes to investigate this WM dysfunction in more detail. This showed that patients performed worse than controls on non-spatial relational binding, with a moderate to large effect size, and marginally worse than controls on spatial relational binding and single-item conditions, with a moderate effect size. There was no significant group difference for the conjunctive binding condition (small effect size). In addition, it seems that specifically the group difference for the single-item condition, and to a lesser extent the non-spatial relational binding condition, is driven by the long delays. While it can be concluded that the medial temporal lobe patients show a general impairment in WM, our planned comparisons should be interpreted with caution. However, inspection of the effect sizes indicates that relational binding is impaired in patients with medial temporal lobe lesions,

whereas conjunctive binding is not. We also found a deficit in the single-item condition, although this was mainly due to a deficit on long-delay trials. It therefore seems that the medial temporal lobe is involved in associative WM as well as in single-item WM, provided that the delay between stimulus presentation and probe is long enough (> 6 s).

However, in line with this notion, we would then also have expected a deficit in long-delay trials for the conjunctive binding condition, similar to the findings in the single-item condition. If conjunctions are established in a rather automatic fashion earlier in the visual stream (Allen, Hitch, Mate, & Baddeley, 2012; Kubovy, Cohen, & Hollier, 1999; Piekema et al., 2006, 2010; Rossi-Arnaud et al., 2006), they are, as a result, like to be processed as single 'unitized' objects. Therefore, conjunctions should also be affected by long delays in the same way as single items. However, the present findings do not show such an effect. This raises the question about load as a key factor. By definition, conjunctive binding results in unified representations, which may require less cognitive load. The discrepancy between conjunctions and single items should be examined to more detail in future studies, possibly by investigating the role of the medial temporal lobe in conjunctive versus non-conjunctive memory during short and long delays using fMRI.

In general, our results can be interpreted in light of Baddeley's episodic buffer (Baddeley, 2012; Repovs & Baddeley, 2006). The episodic buffer integrates information from the slave systems and serves as an interactive system between WM and long-term memory. In addition, it may serve as an overflow storage buffer when the capacity of the slave systems is exceeded (Baddeley, 2012). Although the underlying neural mechanisms of the episodic buffer are still under debate, the hippocampus may be a good candidate (Berlingeri et al., 2008; but see Baddeley, 2012). The hippocampus is found to be involved when WM capacity is exceeded either when the load is large or when the delay period is long (Jeneson et al., 2011). Our results may be interpreted as supporting this notion. However, the episodic buffer has been criticised as it makes the model not very parsimonious (Ruchkin, Grafman, Cameron, & Berndt, 2003) and it is also complicated to develop a task specifically assessing the buffer and its neuroanatomical underpinnings (Gooding, Isaac, & Mayes, 2005).

Alternatively, it could be argued that the medial temporal lobe is merely involved in associative WM due to its role in relational memory (Konkel & Cohen, 2009). That is, it may be the associative aspect as such which explains our results. It is well known that the medial temporal lobe is crucial for episodic memory (Squire, 2009a) and by its nature, episodic memory formation requires the integration of contextual information. As a consequence, it is argued that the medial temporal lobe is essential for processing associative information in general and that the deficit in processing this information is the crucial feature in amnesia

(Mayes et al., 1992). However, this account cannot explain why patients in the current study show delay-specific deficits for single items as well.

Possibly, longer delay lengths evoke long-term memory encoding processes that in itself rely on hippocampal function. As a result, one could argue that long-term memory performance would be better for those items being processed during long delays (especially if no interfering stimuli are presented during the delay), as opposed to items being processed during short delays. We did not examine this in the current study, but a previous study did not find enhanced long-term recall for stimuli presented during longer delays in a WM binding task (Van Geldorp et al., 2012). However, recent fMRI results in healthy participants showed that hippocampal activation during an associative WM task was predictive for long-term memory success, and absent for associations that did not "survive" WM processing (Bergmann et al., 2012). It can therefore be argued that hippocampal activation during WM tasks reflects long-term memory encoding processes.

In line with this idea, Jeneson and colleagues argue that WM performance relies on long-term memory processes in the medial temporal lobe, specifically when WM capacity is exceeded (Jeneson et al., 2011, 2010; Jeneson & Squire, 2012). In the present paradigm, the non-spatial relational binding condition seems more difficult than the other conditions, possibly due to differences in cognitive load (Mitchell, Johnson, Raye, Mather, & D'Esposito, 2000). This would explain why patients show a deficit for this condition: WM capacity is exceeded and they cannot rely on their medial temporal lobe to perform the task. However, we deliberately aimed to keep the cognitive load comparable across task conditions by equalizing the number of features that had to be maintained during each trial. Moreover, using a similar design, Piekema et al. (2010) did not find that non-spatial relational binding was more difficult than the other binding conditions.

In our attempt to keep both stimulus presentation and WM load comparable across task conditions, we inherently made part of the presented material irrelevant to the task. It has been suggested that irrelevant features are involuntarily encoded into WM, irrespective of whether the participant has been notified which features would be probed (Marshall & Bays, 2013). These irrelevant features occupy available resources within WM and make performance decline. However, each trial contained the same amount of relevant and irrelevant features. It is therefore unlikely that the irrelevant features resulted in differential performance across conditions. In addition, it was also shown that the involuntary encoding of irrelevant features did not necessarily lead to involuntary maintenance of those features (Marshall & Bays, 2013). That is, the irrelevant features can be 'dropped' from memory to make place for the relevant features.

A limitation of the present study is that although in all patients the lesion extent included the hippocampus, the lesions were not limited to this region. That

is, it is likely that the perirhinal cortex or other cortical temporal structures have been resected as well. As these regions are important for object processing (Eichenbaum, Yonelinas, & Ranganath, 2007), this may explain the deficit in the single-item condition after a long delay. Unfortunately, in the present study it was not possible to quantify the lesion extent within medial temporal lobe subregions.

In conclusion, patients with unilateral anterior temporal lobectomy are impaired on the present WM task. The results are in agreement with the theory of WM overload. Clearly, we show that the medial temporal lobe is not only involved in WM when the task contains spatial features. Our results are in line with the theory of WM overload. That is, medial temporal lobe involvement during WM tasks is arguably driven by either longer delays or relational associative components.

Chapter 5 The interaction of working memory performance and episodic memory formation in patients with Korsakoff's amnesia

Published as:
Van Geldorp, B., Bergmann, H. C., Robertson, J., Wester, A. J., & Kessels, R. P. C. (2012). The interaction of working memory performance and episodic memory formation in patients with Korsakoff's amnesia. *Brain Research*, *1433*, 98–103. doi:10.1016/j.brainres.2011.11.036.

Abstract

Both neuroimaging work and studies investigating amnesic patients have shown involvement of the medial temporal lobe during working memory tasks, especially when multiple items or features have to be associated. However, so far no study has examined the relationship between working memory and subsequent episodic memory in patients using similar tasks. In this study, we compared patients with amnesia due to Korsakoff's syndrome (n=19) with healthy controls (n=18) on an associative working memory task followed by an unexpected subsequent episodic memory task. The computerized working memory task required participants to maintain two pairs of faces and houses for either short (3 s) or long (6 s) delays. Approximately 5 minutes after completion of the working memory task, an unexpected subsequent recognition task with a two-alternative forced choice paradigm was administered. By directly comparing working memory and subsequent episodic memory, we were able to examine long-term encoding processes that may take place after longer delays. As expected, patients performed at chance level on the episodic memory task. Interestingly, patients also showed significantly impaired working memory performance (p<.01), even at short delays. Longer delays did not result in better subsequent memory, indicating that they do not facilitate long-term encoding processes. Our results are discussed in relation to Baddeley's working memory model as the episodic buffer is assumed to be a short-term store for maintaining bound representations. In light of these results, the long-standing view that working memory and long-term memory are strictly dissociated may need to be revisited.

Introduction

The medial temporal lobe and its connections to the diencephalon are essential for processing relational information (Henke, Weber, Kneifel, Wieser, & Buck, 1999; Mayes, Montaldi, & Migo, 2007; Van der Werf et al., 2003; Visser et al., 1999). This may explain why amnesiacs and older adults show episodic-memory deficits which by nature contain contextual information (Chalfonte & Johnson, 1996; Mayes et al., 1992; Naveh-Benjamin, 2000). However, it is less clear if and how this diencephalic-medial temporal lobe memory circuitry is involved in processing relational information within working memory.

Recent neuroimaging studies reported medial temporal lobe involvement in working memory tasks (Hannula & Ranganath, 2008; Schon, Quiroz, Hasselmo, & Stern, 2009), specifically when information from different sources had to be associated (Davachi & Wagner, 2002; Piekema et al., 2009, 2010). In addition, several studies demonstrated associative working memory deficits in amnesia patients with lesions in the medial temporal lobe and/or diencephalon (Olson et al., 2006; Parra, Abrahams, Fabi, et al., 2009; Piekema et al., 2007; van Asselen et al., 2005). These findings call for studies investigating the functional relationship between working memory and long-term memory. Several neuroimaging studies looked into this potential link and showed that working memory maintenance processes mediated by medial temporal lobe activity are predictive of successful long-term memory formation (Nichols et al., 2006a; Ranganath et al., 2005). Moreover, one study demonstrated that amnesia patients were impaired in maintaining single faces for a period of 7 s (Nichols et al., 2006a). This study also showed that working memory performance at the 7-s delay (but not at a 1-s delay) was related to long-term memory performance, indicating the importance of medial temporal lobe structures in long-term memory formation and in working memory after 7 s.

However, these studies investigated the relation between working memory and long-term memory for single items rather than for associations. Associative working memory was studied by Olson and colleagues (2006) who found that amnesic patients are impaired in maintaining object-location associations for both short (1 s) and long (8 s) delay periods. Nevertheless, this study did not examine working memory performance in relation to episodic memory formation. One patient study found that amnesic patients with hippocampal damage were impaired on a relational-memory task with a continuous recognition paradigm that included both short and long lags (Hannula et al., 2006). Although the use of long lags may promote long-term encoding processes, this paradigm does not enable the examination of subsequent episodic-memory formation.

In the current study, we compared associative working memory with subsequent episodic memory in amnesia patients with dysfunction of the diencephalic- medial

temporal lobe memory system due to Korsakoff's syndrome (Visser et al., 1999). In the working memory task, two house-face pairs were presented and those pairs had to be maintained for either a short (3 s) or a long (6 s) delay. The subsequent episodic memory task required participants to choose which one of two alternative pairs had been presented during the working memory task. Extending previous results (Nichols et al., 2006a; Olson et al., 2006; Parra, Abrahams, Fabi, et al., 2009; Piekema et al., 2007; van Asselen et al., 2005), it was hypothesized that amnesia patients would show deficits not only in subsequent episodic memory, but also in associative working memory. In addition, as item pairs that have been processed during long delays are possibly subjected to long-term encoding (Buffalo et al., 1998), it was hypothesized that control participants would show better subsequent episodic memory for those pairs, in line with the study by Nichols et al. (2006a).

Experimental procedures

Participants

Nineteen patients with severe anterograde amnesia, diagnosed with Korsakoff's syndrome, and 18 healthy controls (see Table 1) participated in the present study. An additional 5 amnesia patients and 2 healthy controls were successfully tested, but performed below chance level (i.e., 50% correct or less) on the associative working memory task. Their data were therefore excluded from further analyses. All patients were recruited from the Korsakoff Clinic of the Vincent van Gogh Institute for Psychiatry, Venray, the Netherlands, and met the criteria for DSM-IV-TR Alcohol-induced persisting Amnesic disorder (American Psychiatric Association, 2000) and the criteria for Korsakoff's syndrome as described by Kopelman (2002). The diagnosis was supported by extensive neuropsychological testing and neuroimaging findings, excluding other etiologies that could have produced the amnesia (i.e. stroke, tumor). None fulfilled Oslin's proposed criteria for alcohol-related dementia (Oslin, Atkinson, Smith, & Hendrie, 1998). General exclusion criteria were use of psychotropic medication and presence of neurological disorders (head injury, coma, epilepsy, etc.).

Healthy volunteers were recruited from the general community and were selected to match the patient group with respect to age, sex and educational level (as classified on a 7-point scale; Verhage, 1964). Additional exclusion criteria for the control group were a history of alcohol abuse or psychiatric disorders (self-report). The study was approved by the Institutional Review Board of the Vincent van Gogh Institute for Psychiatry and all participants provided written informed consent according to the Declaration of Helsinki. Table 1 shows the demographic and clinical characteristics of the participants that were included in analyses. All participants had normal or corrected to normal vision.

Table 1 Demographical and Clinical Characteristics for all Participants

	Healthy controls	Korsakoff's amnesia	Statistic	*P*-value
Number of participants (m:f)	18 (14:4)	19 (15:4)		
Age (Mean, SD)	52.22 (8.57)	53.47 (8.27)	$t(35)=.45$	.65
Educational level (Mode, range)	5 (2-6)	4 (2-6)	Mann-Whitney $U=107.50$	.053
WAIS III Digit Span (Mean, SD)	6.33 (0.91)	5.58 (1.90)	$t(35)=-1.53$	.14
CVLT total score 1-5 (Mean, SD)	55.28 (1.39)	26.47 (5.03)	$t(35)=-16.03$	<.001
CVLT B-list (Mean, SD)	7.06 (0.41)	3.42 (0.28)	$t(35)=-7.42$	<.001
CVLT free Recall (Mean, SD)	12.78 (0.52)	1.58 (0.39)	$t(35)=-17.42$	<.001
CVLT cued Recall (Mean, SD)	13.00 (0.49)	3.58 (0.45)	$t(35)=-14.29$	<.001
CVLT recognition (Mean, SD)	42.00 (1.72)	32.83 (2.71)	$t(34)=-12.14$	<.001
TMT-A, s (Mean, SD)	-	53.62 (21.78)	-	-
TMT-B, s (Mean, SD)	-	72.26 (47.25)	-	-
TMT-C, s (Mean, SD)	-	116.06 (73.71)	-	-
TMT interference (Mean, SD)	-	91.29 (59.43)	-	-
Stroop-I, s (Mean, SD)	-	55.30 (13.34)	-	-
Stroop-II, s (Mean, SD)	-	71.20 (19.96)	-	-
Stroop-III, s (Mean, SD)	-	139.00 (85.09)	-	-
Stroop interference (Mean, SD)	-	109.81 (69.33)	-	-

Material and procedure

All participants completed a short neuropsychological examination, consisting of the Dutch version of the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) and the WAIS-III Digit Span (D. Wechsler, 1997). Additional information was available for the patient group, including test performance on the Stroop Color Word Test (Stroop, 1935) and Trail Making Test (Reitan, 1985).

Neuropsychological testing revealed that WAIS-III Digit Span scaled score did not significantly differ between amnesia patients and healthy controls. Only 2 patients performed in the impaired range (i.e. over 2 standard deviations below average). For Stroop interference and Trail Making Test interference, 2 and 4 patients respectively performed in the impaired range. In contrast, all patients were severely impaired on episodic memory as measured by the CVLT.

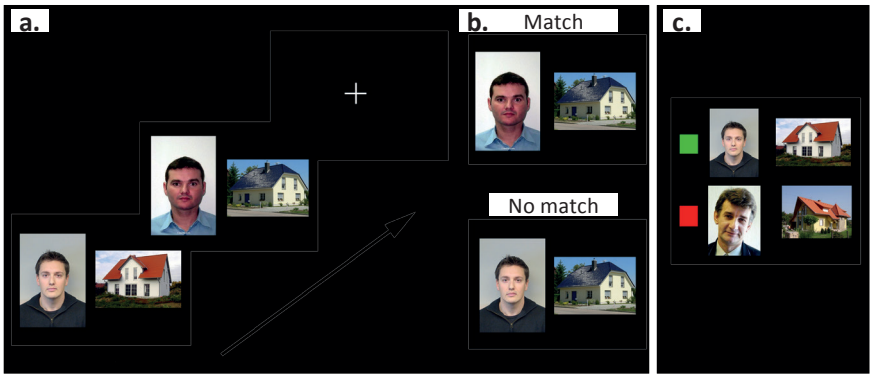

Figure 1 Schematic overview of the experiment. (**a**) The associative working memory task. Two face-house stimulus pairs are presented followed by a delay interval of either 3 or 6 s. (**b**) Immediately after this delay, a probe is presented. The probe can either be a match or a non-match (i.e. a recombination of a face and house from that trial). (**c**) After approximately 5 minutes, the subsequent memory was administered. This task requires participants to respond by button press which combination they had encountered before in the working memory task.

Working memory task

All participants completed a computerized delayed match-to-sample associative working memory task that required participants to maintain two house-face combinations in each trial (see Figure 1). This working memory task is based on a task used by Piekema et al. (2009) in a neuroimaging study that showed greater hippocampal activation for house-face associations during encoding than for house-house or face-face associations. The task was adjusted for usage in patients by reducing the number of trials and shortening delay intervals.

The stimulus set consisted of pictures of male faces with a neutral expression and pictures of similar sized detached houses. The stimuli were presented left (face) and right (house) of the center of the screen of a 15.4-inch Dell XPS M1530 laptop. The probe was presented after a maintenance interval of either 3 or 6 s, and was a match in half of the cases and a non-match in the other half. A match is one of the stimulus pairs as shown in that trial and a non-match is an intra-trial recombination of stimuli in that trial. The latter was to prevent responses on the basis of familiarity. Match trials were randomly assigned to be the first or the second studied pair and were on average equally often the first or the second studied pair. Participants were asked to decide whether the probe was a match or a non-match using two (green and red colored) buttons on a button box. Four

blocks consisting of 10 trials each (8 experimental trials and 2 catch trials) were completed. Each block included two catch trials (2 per block) to prevent participants from using a strategy of maintaining only one of the two pairs. Catch trial 1 is a normal trial as described above, but catch trial 2 shows a probe that is a recombination of one item from the current trial with one item from the previous trial. Participants using the strategy would perform well on catch trial 1, but badly on catch trial 2. Only one healthy control participant and one patient appeared to use this strategy (indicated by a performance drop of more than 50%). Hence, strategy use is not considered a major problem, and as a result, no data were excluded.

Subsequent episodic memory task

After an unfilled delay of approximately 5 minutes, participants performed an unexpected subsequent episodic memory task with four blocks of 8 trials each. With a two-alternative forced choice paradigm, participants were asked to decide which of the two simultaneously presented pairs had been presented previously in the working memory task. The non-match pair consisted of a recombination of any two stimuli from the working memory task stimulus set. The match pair was always a pair that had not already been shown as a probe in the working memory task, to prevent familiarity-based responses: working memory probe pairs would have generated higher familiarity, as they had already been shown twice as a pair. For both tasks the percentage of correct answers was measured. Since each trial has two optional responses, chance level is indicated by a 50% performance.

An alpha of .05 was used in all analyses. For all analyses, effect sizes (η_p^2) were computed that describe the proportion of variance explained by the factor in question, independent of the other variables.

Results

A 2 (Group: patients vs. controls) x 2 (Condition: working memory vs. subsequent episodic memory) x 2 (Delay: short vs. long) repeated measures ANOVA was performed to analyze the data. This analysis revealed that, in general, patients performed significantly worse (M = 57.4) than controls (M = 71.0), $F(1,35) = 26.70$, $p < .001$, $\eta_p^2 = .43$ (see Figure 2). In addition, a significant performance difference between the working memory task and the subsequent episodic memory task was found ($F(1,35) = 55.80$, $p < .001$, $\eta_p^2 = .61$), with participants scoring higher on the working memory task (M = 73.8) than on the subsequent memory task (M = 54.6).

No effect of Delay was observed ($F(1,35) = 1.47$, $p = .23$, $\eta_p^2 = .04$). Our hypothesis regarding long-term encoding predicted a difference in episodic memory

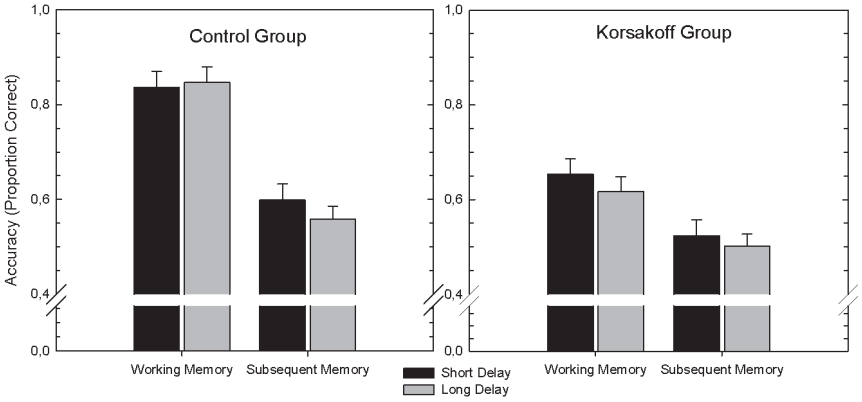

Figure 2 Means and standard errors of performance on the associative working memory task and the subsequent memory task, for both controls and the Korsakoff patients.

performance for item pairs that had been processed during short delays as compared to pairs that had been processed during long delays. However, a paired samples t-test revealed no significant difference between those conditions in healthy controls ($t(17) = 1.05$, $p=.31$), indicating no relation between working memory delay length and long-term memory performance.

The interaction effect of Group by Condition was significant ($F(1,35) = 7.40$, $p=.01$, $\eta_p^2 = .18$), reflected in the smaller group difference for the subsequent memory task than for the working memory task. Patients performed significantly worse than controls on the working memory task ($t(35)=-5.05$, $p<.01$), but working memory performance was above chance level for both healthy controls ($t(17)=10.40$, $p<.01$) and patients ($t(18)=5.35$, $p<.01$). Compared to the working memory task, both groups showed a strong decrease in performance on the subsequent memory task; however, healthy controls still performed above chance level ($t(17)=2.66$, $p=.02$), whereas patients did not ($t(18)=.77$, $p=.45$). This floor level performance in patients prevents the possibility for a larger group difference. No other significant interaction effects were found (all Fs<1).

In addition, we examined the effect of the degree of familiarity of the individual items in the subsequent memory task. The fact that matching working memory probe pairs were not used in the subsequent memory task does not preclude the fact that individual items could have been presented during the working memory probe phase. This means that different levels of familiarity are possible for each trial. In total, four items were simultaneously presented in the subsequent memory task. Of these four items, the participant could have encountered zero, one, two or three items that were shown twice in the working memory task.

Only sporadically were 0 or 3 familiar items presented (on average 3 and 5 trials per participant, respectively) and when these items were excluded from analyses, the results described above did not change. In order to examine whether different levels of familiarity influenced performance, we used a 2 (Group: patients vs. controls) x 2 (level of familiarity: 1 vs. 2) repeated measures ANOVA. It was revealed that performance did not significantly differ over the different levels of familiarity ($F<1$). In addition, the group by level of familiarity interaction effect was not significant ($F<1$).

Discussion

The present study shows that in addition to their episodic memory deficit, patients with severe amnesia are significantly impaired in associative working memory, compared with healthy controls, even for delays as short as 3 s. There was no effect of delay and delay length did not influence long-term memory performance.

On the basis of previous research suggesting that maintaining items over long delays recruits long-term encoding processes (Buffalo et al., 1998; Nichols et al., 2006a), we hypothesized that healthy controls would show better subsequent memory performance for long-delay item pairs than for short-delay item pairs. However, delay length in the working memory task was unrelated to long-term memory performance in healthy participants. This suggests that, in our study, longer delays did not facilitate long-term encoding to the extent that it would be reflected by an increased subsequent-memory performance.

As discussed, one possible confound is that the level of familiarity of individual items in the subsequent memory task may vary. However, we showed that familiarity did not influence performance, which suggests that differences in the level of familiarity of individual items have not confounded our results. It could also be argued that patients with Korsakoff's syndrome have frontal lobe damage, resulting in executive dysfunction or working memory deficits, thereby providing an alternative explanation for the observed impaired performance. However, neuropsychological examination revealed that only very few patients performed in the impaired range on the Stroop interference, Trail Making Test interference and Digit Span. In addition, Stroop and Trail Making Test interference scores did not correlate significantly with working memory performance. Hence, we argue that executive or attentive dysfunction cannot explain the observed pattern of results.

Concerning the time course of working memory impairments in amnesia patients, previously reported results are mixed. For example, some studies demonstrated no effect of delay (Olson et al., 2006), whereas others did demonstrate such an effect

(i.e., Buffalo et al., 1998). Our current findings offer an explanation for these seemingly discrepant findings. That is, working memory for single items is generally found to be impaired only after longer (i.e. >6 s) maintenance periods (Buffalo et al., 1998; Nichols et al., 2006a; Piekema et al., 2007). In turn, working memory deficits for associations seem to be present irrespective of delay length, as supported by the present study and previous work by Olson *et al*. (2006). Hence, it may be argued that in working memory, multiple items or features always rely on diencephalic-medial temporal lobe processing, whereas single items are only processed in medial temporal lobe structures when the delay length is long.

These results suggest that different memory functions cannot be strictly related to separate brain structures. Hannula and Ranganath (2008) propose an alternative way to define memory and its associated brain structures. They suggest that brain structures are better described in terms of their functions instead of in terms of consciousness (declarative versus nondeclarative) or length of retention interval (short-term memory versus long-term memory). The hippocampus is suggested to rapidly encode associations (Henke, 2010), which is in line with neuroimaging studies showing that the hippocampus is involved in processing associations rather than single items or features (Henke et al., 1997; Mitchell, Johnson, Raye, & D'Esposito, 2000). This processing mode is recruited by the paradigm used in the present study and underlies episodic memory formation.

On a functional level, our findings may be interpreted in the light of Baddeley's (2007) episodic buffer as it is assumed to be a short-term store for maintaining bound representations. Moreover, the episodic buffer functions as an overload buffer when the capacity of the slave systems is exceeded. Accordingly, the episodic buffer may come into play when working memory tasks involve binding processes or when items have to be maintained for longer delay periods. The relation between the episodic buffer and long-term memory remains unclear, but the current study provides no support for a strict independence of working memory and long-term memory. Possibly, the episodic buffer may subserve an interactive process linking these two memory systems. The anatomical representation of the episodic buffer is also under debate. Although the hippocampus seems an obvious candidate (see e.g. D. Luck et al., 2010), Baddeley et al. (2011) find no evidence for hippocampal involvement in binding by describing a patient with a specific hippocampal deficit who shows no impairment on several binding tasks. Future studies may provide more insight into the episodic buffer, its functions and anatomical representation. In summary, patients with severe Korsakoff's amnesia are significantly impaired in an associative working memory task. To our knowledge, this is the first study to demonstrate associative working memory problems in amnesia patients at such a short interval. In addition, there are no patient studies that have investigated associative working memory in combination with subsequent episodic memory

using similar tasks. Our results indicate that working memory and long-term memory may not be strictly independent as assumed (Squire, 2009a). That is, the diencephalic- medial temporal lobe circuit is also involved in working memory processes, in addition to long-term memory function (see also Ranganath & Blumenfeld, 2005).

Although it was not the aim of the present study to make specific claims on the neural representation of working memory binding in detail, our results suggest that the diencephalic- medial temporal lobe memory circuit is involved in associative working memory irrespective of delay length. Future neuroimaging studies in both patients and healthy participants could clarify the exact underlying neural basis of associative working memory and its relation to episodic memory.

Chapter 6 Working memory binding and episodic memory formation in normal aging, Mild Cognitive Impairment and Alzheimer's dementia

Submitted as:
Van Geldorp, B., Heringa, S.M., Van den Berg, E., Olde Rikkert, M.G.M., Biessels, G.J., Kessels, R.P.C. Working memory binding and episodic memory formation in normal aging, Mild Cognitive Impairment and Alzheimer's dementia.

Abstract

Recent studies indicate that medial temporal lobe (MTL) dysfunction hampers working memory (WM) performance, especially when associations have to be maintained. However, most studies typically do not assess the relationship between WM and episodic memory formation. In the present study, we examined WM and episodic memory formation in normal aging and in patients with early Alzheimer's disease (mild cognitive impairment [MCI] and Alzheimer's dementia [AD]), who are likely to have medial temporal lobe dysfunction.

In the first study, 26 young adults (mean age 29.6) were compared to 18 middle aged adults (mean age 52.2) and 25 older adults (mean age 72.8). We used an associative WM task, which requires participants to maintain two pairs of faces and houses for short (3 sec) or long (6 sec) delays. After the WM task, an unexpected subsequent memory task was administered. In the second study, 27 patients with AD and 19 patients with MCI were compared to 25 older controls, using the same paradigm as in study 1.

Older adults performed worse than both middle aged and young adults. No effect of delay was observed and pairs that were processed during long delays were not better remembered in the subsequent memory task. Both patient groups performed significantly worse than controls on the episodic memory task as well as the associative WM task.

Aging presents with a decline in WM binding, a finding that extends similar findings in episodic memory. Longer delays in the WM task did not facilitate episodic memory formation. However, WM and episodic memory may not be independent systems. We suggest that MTL dysfunction results in WM deficits when WM capacity is exceeded, for example by associative processes.

Introduction

Patients with early Alzheimer's Disease (AD) have profound long-term memory problems (McKhann et al., 2011; Petersen et al., 1999), largely due to hippocampal atrophy (Small, Schobel, Buxton, Witter, & Barnes, 2011). However, it is less clear to what extent working memory is affected. Standard neuropsychological tests often reveal no deficits (Guarch et al., 2008; Kramer et al., 2006), but recent studies have shown that the medial temporal lobe (MTL) may be involved in working memory, especially when multiple items or features have to be associated (i.e. binding). For example, lesion studies show that patients with damage to the hippocampus or surrounding MTL structures have deficits in maintaining bound information over short periods of time (Braun et al., 2011; Della Sala et al., 2012; Hannula & Ranganath, 2008; Jeneson et al., 2010; Olson et al., 2006; Van Geldorp, Bouman, Hendriks, & Kessels, 2014a). In addition, neuroimaging studies found activation in the hippocampus and related MTL structures, when assessing working memory binding (Hannula & Ranganath, 2008; D. Luck et al., 2010; Mitchell, Johnson, Raye, & D'Esposito, 2000; Piekema et al., 2006, 2009, 2010).

Several explanations have been offered regarding the exact role of the MTL in working memory binding. First, the MTL may be involved in working memory binding because of its important role in relational memory in general (Cohen et al., 1999; Eichenbaum et al., 1994; Konkel & Cohen, 2009). Second, it could be argued that the MTL activity reflects incidental long-term encoding processes, already ongoing during working memory tasks (Ezzyat & Olson, 2008; Ranganath et al., 2005). Finally, it has been argued that the MTL is only involved in working memory tasks when working memory capacity is exceeded (Jeneson et al., 2011, 2010; Jeneson & Squire, 2012), for example when set sizes or delay periods increase. Recently, we examined these explanations in a study in patients with diencephalic hippocampal amnesia due to Korsakoff's syndrome, testing both working memory binding and subsequent episodic memory (Van Geldorp et al., 2012). In this study, participants were required to maintain two house-face pairs over a delay period of either 3 or 6 seconds. After the working memory task, an unexpected subsequent memory task was administered. Delay length was varied, hypothesizing that longer delays may induce more incidental long-term encoding processes (Buffalo et al., 1998; Nichols et al., 2006a). In addition, longer delays may result in working memory capacity to be exceeded, causing MTL involvement. We reported that these amnesia patients showed deficits in working memory binding, both over short and longer delays. Moreover, longer delays did not result in improved subsequent memory performance. Therefore, no evidence was found for the hypothesis that involvement of the diencephalic-MTL memory circuit in working memory binding reflects long-term processes (Van Geldorp et al., 2012).

Here, we extend our previous research with two additional studies focusing on normal and pathological age-related memory (dys)function. The first part of this paper describes an aging study, in which we examined how the interaction between working memory and episodic memory formation develops across age. We hypothesized that both working memory and episodic memory would decline with age (Salthouse, 1990, 2010). By directly comparing working memory and episodic memory performance, using similar tasks, we are able to examine long-term encoding processes that may take place (Buffalo et al., 1998; Nichols et al., 2006a). Item pairs that have been processed during long delays are possibly subjected to long-term encoding processes. Therefore, we examine whether healthy (especially young) adults show an expected facilitating effect of long delays on long-term encoding. Healthy young adults were not included in our previous study (Van Geldorp et al., 2012), while they may have more working memory resources to complete the task. Thus, we hypothesized that items that are processed during long delays are better subsequently remembered in this young adult group. In addition, we compared the young adult group performance with two older healthy groups (i.e., middle aged and elderly participants).

Secondly, we aimed to replicate our previous findings using the same paradigm in patients with early Alzheimer's disease (mild cognitive impairment [MCI] and Alzheimer's dementia [AD]). Patients with alcoholic Korsakoff's syndrome regularly have frontal damage (Brokate et al., 2003) and comorbid psychiatric disorders (notably addiction), which also may have had an effect on working memory performance. Although we consider it unlikely that this can fully explain our previous results, we argue that in the present group of patients frontal lobe deficits are less prominent, especially in the MCI group. We expect patients to be impaired not only on the subsequent episodic memory task, but also on the working memory binding task. In line with the first study, we examine whether controls show better episodic memory performance for item pairs that were processed during long delays, as opposed to item pairs that are processed during short delays.

Study 1

Participants

Three groups of healthy adults participated in this study: a group of 26 young adults, a group of 18 middle aged adults and a group of 25 older adults. Exclusion criteria were subjective memory complaints and a history of neurological or psychiatric disease. For more detailed information on the group characteristics, see table 1. Note that the group of middle aged adults is the same group as described in Van Geldorp et al. (2012).

Table 1 Demographical and Clinical Characteristics for all Participants of Study 1

	Young adults	Middle Aged	Older adults	Statistics, *p*	Specification
N	26	18	25		
Age (Mean, SD)	29.58 (2.23)	52.22 (8.57)	72.84 (5.45)		
Sex (F/M)	12/14	4/14	17/8	χ^2 (2)=8.84, p=.01	
Education level (Mode, range)[a]	7 (5-7)	5 (2-6)	6 (2-7)	χ^2 (2)=16.97, p<.001	Young>Middle<Old
NART score (Mean, SD)	79.70 (7.61)	79.18 (10.80)	85.09 (13.11)	F (2,63)=2.10, n.s.	
NART IQ-score (Mean, SD)	93.96 (7.47)	103.61 (9.83)	116.22 (19.58)	F (2,64)=16.88, p<.001	Young<Middle<Old

[a] Education level is assessed using the seven categories from Verhage (1964), with 1 = less than primary school and 7 = academic degree

Two additional middle aged adults and three additional older adults were successfully tested, but performed below chance level on the working memory task (cf. Van Geldorp et al., 2012). All participants provided written informed consent.

Paradigm

The paradigm used in this study has been described previously in Van Geldorp et. al. (2012). In short, the working memory task was a delayed match-to-sample associative working memory task that required participants to maintain two house-face combinations over a short delay in each trial (see figure 1). The task consisted of four blocks of eight trials each. The delay period was either 3 s or 6 s and was followed by a probe that could either be a match or no match (intra-trial recombination in order to prevent familiarity-based responses).

Approximately five minutes after completing the working memory task, the patients performed an unexpected subsequent recognition memory task (a two-alternative forced-choice task, which is also described in van Geldorp et al. (2012) and depicted in figure 1).

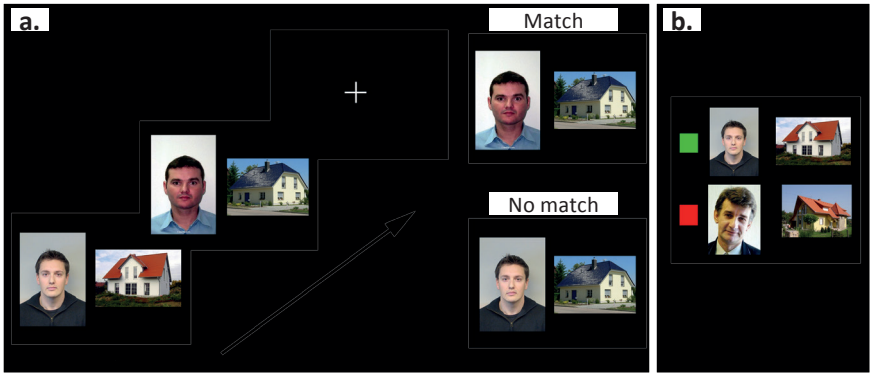

Figure 1 Schematic overview of the experiment. (**a**) The working memory task requires participants to maintain two face-house stimulus pairs. The delay interval is either 3 or 6 seconds. Immediately after this delay, a probe is presented. The probe can either be a match or a non-match (i.e. a recombination of a face and house from that trial). (**b**) The subsequent memory task requires participants to decide which combination they had encountered before in the working memory task.

Analyses

The proportion of correct answers was measured in both tasks. As each test probe has two optional responses, chance level performance would be a score of .50. An alpha of .05 was used in all analyses. A 3 (Group: young adults; middle aged adults; older adults) x 2 (Task: working memory vs. subsequent episodic memory) x 2 (Delay: short vs. long) repeated measures ANOVA was performed to analyze the data. A paired samples t-test was used in order to examine our hypothesis regarding

the long-term encoding. In this analysis, episodic memory performance for short-delay items was compared to episodic memory performance for long-delay items in each group. For all analyses, effect sizes (η_p^2) were computed that describe the proportion of variance explained by the factor in question, independent of the other variables.

Results

The results for study 1 are displayed in Figure 2. All groups performed significantly above chance level in the working memory task (all *p*-values <.001). In the subsequent memory task, the young, middle aged and older adults performed significantly above chance level ($t(25)=6.64$, $p<.001$, and $t(17)=2.66$, $p=.01$, $t(24)=1.83$, $p=.04$, respectively, one-tailed).

As can be seen in Table 1, the middle aged adults were slightly less educated (education level was scored using the seven categories from Verhage, 1964) than both young (Mann-Whitney $U=67.5$, $p<.001$) and older adults (Mann-Whitney $U=132.5$, $p=.02$). Importantly, education level did not significantly correlate with performance on the working memory task ($\varrho=.15$, $p=.20$). However, it did correlate significantly with performance on the subsequent memory task ($\varrho=.28$, $p=.02$). We believe that this has not influenced our results. If anything, middle aged adults' performance on the subsequent memory task would have been better if they were higher educated. This would not have changed the conclusions drawn from our results.

For the effect of sex, we only considered the group of young adults, since this is the only group with an evenly distributed number of males and females. Taking into account the other groups would also allow age and education to influence the effect. A multivariate ANOVA showed that sex distribution did not affect performance on the working memory task ($F(1,24)=0.23$, $p=.64$) or the subsequent memory task ($F(1,24)=3.36$, $p=.08$). Therefore, no covariates were included in the analyses.

The 3-by-2-by-2-repeated measures ANOVA analysis revealed a significant main effect of Group ($F(2,66) = 15.43$, $p <.001$, $\eta_p^2 = .32$). In more detail, older adults performed significantly worse ($M=.63$, $SE=.017$) than both middle aged adults ($M=.71$, $SE=.020$, $p=.008$) and young adults ($M=.76$, $SE=.016$, $p<.001$). The young and middle aged adults did not significantly differ from each other ($p=.18$). In addition, a significant main effect of Task condition was found ($F(1,66)=132.42$, $p<.001$, $\eta_p^2=.67$), with participants scoring higher on the working memory task ($M=.81$) than on the subsequent memory task ($M=.59$). However, the interaction between Group and Task condition was not significant ($F(2,66)=1.23$, $p=.30$, $\eta_p^2=.04$).

No effect of Delay was observed ($F(1,66)<1$, $p=.94$, $\eta_p^2=.0008$). Also, both the interaction effect of Delay * Task condition and the interaction effect of Delay *

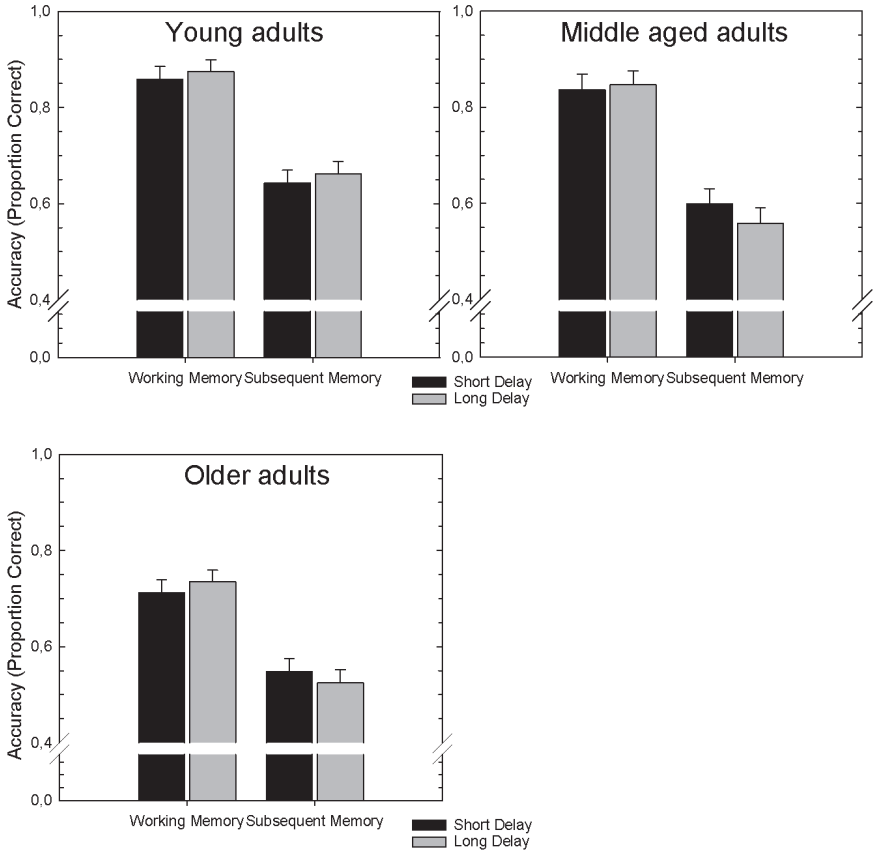

Figure 2 Results for study 1, displaying the mean scores and standard errors of proportion correct answers for young, middle aged and older adults over both delay lengths, separated by condition.

Group were not significant ($F(1,66)=1.86$, $p=.18$, $\eta_p^2=.03$ and $F(2,66)<1$, $p=.53$, $\eta_p^2=.02$, respectively). We had an a-priori hypothesis regarding long-term encoding processes, predicting that item pairs that had been processed during long delays in working memory would be remembered more often in episodic memory as compared to pairs that had been processed during short delays. However, the paired samples *t*-test showed no significant difference between short and long-delay pairs in episodic memory for any of the groups (all *p*-values >.30).

Discussion

The results show that performance declines with age, although only significantly with old age. There was no evidence that aging had a stronger effect on episodic memory than on working memory performance. However, although statistically significant, performance of the older adults was only slightly above chance level for the subsequent memory task, suggesting a possible floor effect. This may have prevented any larger differences between groups, leading to an underestimation of the decline in old age.

The absence of a delay effect suggests that an increase in working memory load does not have a detrimental effect on performance in these groups. Our hypothesis that pairs processed during a long-delay period would be better remembered in the subsequent memory task was not confirmed. That is, longer delays do not result in increased episodic memory formation, even in young adults.

Study 2

Participants

A total of 50 patients with early-stage Alzheimer's disease were included in this study. Patients were recruited via the memory clinic at the department of geriatrics of the Radboud University Nijmegen Medical Centre and the departments of geriatrics and neurology of the University Medical Center Utrecht. Nineteen patients were diagnosed with mild cognitive impairment due to Alzheimer's disease (aMCI; according to the criteria by Petersen et al., 1999) and another group of 27 patients were diagnosed with Alzheimer's dementia (AD; according to the criteria by McKhann et al., 2011). Diagnosis was based on neuroradiological findings (i.e. presence of medial temporal lobe atrophy, absence of vascular lesions or extensive white matter abnormalities), psychiatric and neurological examination and extensive neuropsychological assessment. Standard neuropsychological tests were administered, i.e., the Mini-Mental State Examination (MMSE; Tombaugh & McIntyre, 1992), Wechsler Adult Intelligence Scale – III Digit Span (D. Wechsler, 1997), Trail Making Test (TMT; Reitan, 1985), Stroop Color Word Test (Stroop, 1935), Rey Auditory Verbal Learning test (RAVLT; Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2005), Visual Object and Space Perception (VOSP; Elizabeth K Warrington, James, & Thames Valley Test Company, 1991), and the Letter Digit Substitution Test (LDST; van der Elst, van Boxtel, van Breukelen, & Jolles, 2006). Exclusion criteria for all participants (including the controls) were subjective memory complaints and a history of neurological or psychiatric disease. Patients with a clinical dementia rating >1 (Morris, 1993) or a MMSE-score <20 (Tombaugh & McIntyre, 1992), indicative of a more advanced stage of dementia, were also excluded.

Table 2 Demographical and Clinical Characteristics for all Participants of Study 2

	AD group	MCI group	Control group	Statistics, *p*	Specification
N	27	19	25		
Age (Mean, SD)	76.57 (9.27)	74.37 (7.69)	72.84 (5.45)	F (2,68)=1.55, n.s.	
Sex (F/M)	12/15	9/10	17/8	χ^2 (2)=3.30, n.s.	
Education level (Mode, range) [a]	4 (2-7)	4 (3-7)	6 (2-7)	χ^2 (2)=9.59, p=.01	AD<MCI=Control
MMSE (Mean, SD)	24.85 (2.69)	27.68 (2.31)	28.48 (1.39)	F (2,68)=19.32, p<.001	AD<MCI=Control
Working memory					
WAIS-III Digit Span					
Forward (Mean, SD)	8.33 (1.92)	8.79 (1.81)	9.32 (2.51)	F(2,68)=1.40, n.s.	
Backward (Mean, SD)	4.70 (1.51)	5.58 (1.68)	6.64 (1.75)	F(2,68)=9.00, p<.001	AD<Control
Total (Mean, SD)	13.04 (2.94)	14.37 (3.02)	15.96 (3.78)	F(2,68)=5.15, p<.01	AD<Control
Executive function					
Trail making test					
TMT-A (seconds, SD)	86.94 (54.95)	57.74 (20.69)	45.00 (15.28)	F(2,66)=8.38, p=.001	AD>MCI=Control
TMT-B (seconds, SD)	241.63 (90.42)	174.11 (93.37)	98.48 (55.24)	F(2,66)=19.24, p<.001	AD>MCI>Control
Stroop test					
Stroop I (seconds, SD)	62.04 (20.66)	57.59 (11.97)	-	F(1,39)=0.64, n.s.	
Stroop II (seconds, SD)	89.83 (27.10)	77.76 (20.17)	-	F(1,39)=2.42, n.s.	
Stroop III (seconds, SD)	167.25 (63.59)	158.35 (80.86)	-	F(1,39)=0.33, n.s.	
Interference (Mean, SD) [b]	91.31 (65.60)	86.68 (71.41)		F(1,39)=0.05, n.s.	

Table 2 Continued

	AD group	MCI group	Control group	Statistics, *p*	Specification
Long-term memory					
RAVLT					
Trials 1-5 (Mean, SD)	21.22 (7.73)	26.11 (7.42)	37.44 (11.87)	F(2,66)=19.61, p<.001	AD=MCI<Control
Delayed recall (Mean, SD)	1.92 (2.23)	2.63 (2.27)	6.17 (3.00)	F(2,65)=19.11, p<.001	AD=MCI<Control
Perception					
VOSP[d]					
Letters (Mean correct, SD)	18.00 (2.04)	19.1 (0.80)	-	F(1,39)=7.29, p=.01	AD<MCI
Dots (Mean correct, SD)	9.25 (0.99)	9.82 (0.40)	-	F(1,39)=5.12, p=.03	AD<MCI
Speed					
LDST[e] (Mean correct at 60s, SD)	17.50 (5.93)	25.76 (6.36)	-	F(1,39)=18.22, p<.001	AD<MCI

[a] Education level is assessed using the seven categories from Verhage (1964), with 1 = less than primary school and 7 = academic degree
[b] The Stroop Interference score is calculated as follows: Stroop III – ([Stroop I + Stroop II]/2).
[c] RAVLT: Rey Auditory Verbal Learning test (Van der Elst et al., 2005)
[d] VOSP: Visual Object and Space Perception (Elizabeth K Warrington et al., 1991)
[e] LDST: Letter Digit Substitution Test (van der Elst et al., 2006)

Twenty-five healthy older controls were recruited from the local community and were matched with the patient groups for age ($F(2,68)=1.55$, $p>.05$). Note that the control group is the same group of participants as the group of older adults in study 1. The controls also performed the Digit Span, TMT and RAVLT. Demographics and test scores of both patient groups and the control group are described in table 2. Ten additional participants were tested (four patients with AD, three patients with MCI and three controls), but were excluded because they performed below chance level on the working memory task (cf. Van Geldorp et al., 2012).

Paradigm

The paradigm is identical to the paradigm in study 1, see methods section of study 1.

Analyses

The analyses are similar to the analyses in study 1. A 3 (Group: AD; MCI; controls) x 2 (Task: working memory vs. subsequent episodic memory) x 2 (Delay: short vs. long) repeated measures ANOVA was performed to analyze the data. Again, a paired samples *t*-test was used in order to examine our hypothesis regarding the long-term encoding, by comparing episodic memory performance for short-delay items was to episodic memory performance for long-delay items in each group. For all analyses, effect sizes (η_p^2) were computed that describe the proportion of variance explained by the factor in question, independent of the other variables.

Results

The results are displayed in Figure 3. All groups performed significantly above chance on the working memory task (all *p*-values <.001). In the subsequent memory task, performance of both the AD and the MCI group did not significantly exceed chance level ($t(26)=-1.14$, $p=.14$, and $t(18)=0.50$, $p=.31$, respectively, one-tailed). Controls performed only slightly above chance level $t(24)=1.83$, $p=.04$, one-tailed).

As can be seen in Table 2, a significant difference between groups was found with respect to education level (assessed using the seven categories from Verhage, 1964). Similar to study 1, education level did not significantly correlate with performance on the dependent variables (performance on the working memory task [$\varrho=.18$, $p=.13$] and on the subsequent memory task [$\varrho=.17$, $p=.15$]). Hence, we did not include education as a covariate in the analyses.

The 3-by-2-by-2-repeated measures ANOVA analysis revealed a significant main effect of Group ($F(2,68)=6.07$, $p=.004$, $\eta_p^2=.15$). In more detail, controls performed significantly better ($M=.63$, $SE=.014$) than the AD group ($M=.57$, $SE=.013$, $p=.004$) and marginally better than the MCI group ($M=.58$, $SE=.015$, $p=.07$). The patient groups did not significantly differ ($p>.9$). In addition, a significant main effect of Task was found ($F(1,68)=74.51$, $p<.001$, $\eta_p^2=.52$), with participants scoring higher on the

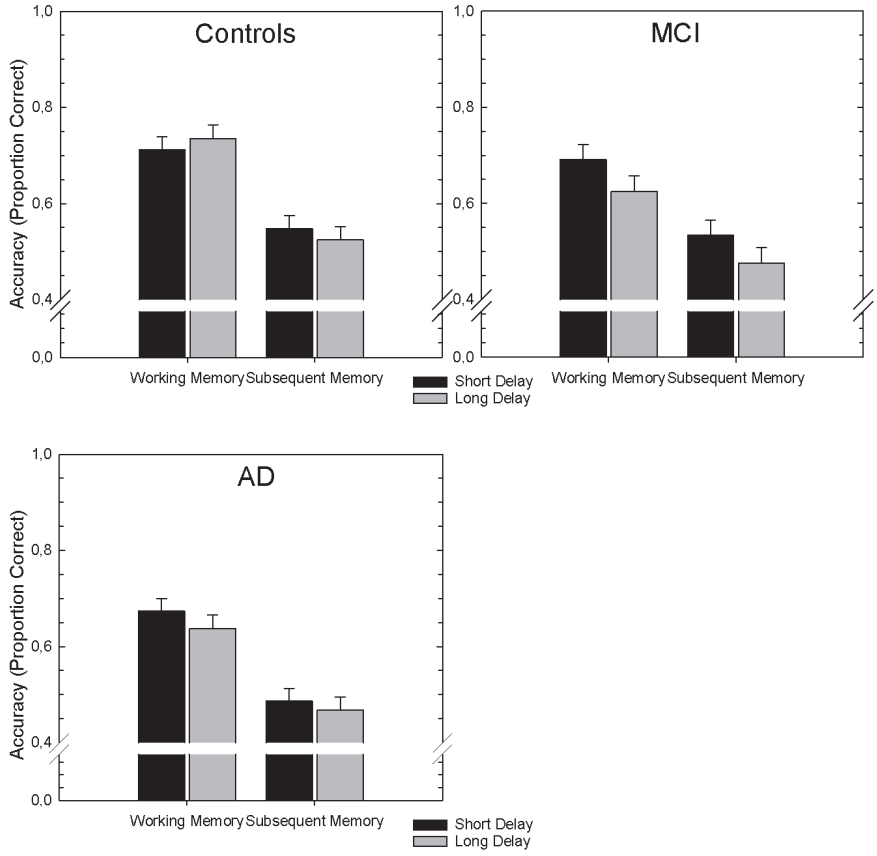

Figure 3 Results for study 2, displaying the mean scores and standard errors of proportion correct answers for patients and controls over both delay lengths, separated by condition.

working memory task (M=.68) than on the subsequent memory task (M=.51). However, the interaction between Group and Task condition was not significant ($F(2,68)<1$, p=.80, η_p^2=.006).

A significant effect of Delay was observed ($F(1,68)$=4.57, p=.03, η_p^2= .06), with participants scoring higher when the delay was short (M=.61) than when the delay was long (M=.58). Both the interaction effect of Delay * Task condition and the interaction effect of Delay * Group were not significant ($F(1,68)<1$, p=.83, η_p^2=.001 and $F(2,68)$=1.52, p=.23, η_p^2=.04, respectively). Considering the a-priori hypothesis regarding long-term encoding processes, we observed no significant difference between short and long-delay pairs in episodic memory for healthy controls ($t(24)$ = -1.10, p=.28).

Discussion

The results show that the patient groups are impaired on both the subsequent memory task and working memory binding task. In line with our hypothesis, this shows that patients with a condition that is characterized by medial temporal lobe dysfunction have a working memory deficit. No difference in performance was observed between patients with AD and patients with MCI. This may be due to a selection bias, since only AD patients in the early stages were included. In more advanced AD patients, a further decline in working memory performance is expected. With respect to the neuropsychological examination, differences were mainly observed in non-memory domains (see Table 2). Alternatively, the absence of a difference between MCI and AD patients on the working memory task in combination with a similar performance on episodic memory tests may indicate that the deficit in long-term memory encoding produces the associative working memory deficit.

As noted before, the controls performed only slightly above chance level in the subsequent memory task. Therefore, we cannot draw firm conclusions about patients' performance on this task as there seems to be a floor effect. The difference between controls and patients might have been underestimated, and it may be that a less difficult task reveals a Group by Task interaction effect. However, we believe that the most important finding here is that patients are impaired in the working memory binding task, where no floor effect is present.

In contrast to study 1, this study shows that a longer delay does significantly affect performance. This is also in agreement with the notion that working memory capacity was exceeded in these groups, when the delay period was extended. Note that there was no interaction effect between Delay and Group, possibly because of limited statistical power. In the present study we could thus not show that a longer delay affects patients to a greater extent than healthy older controls. However, both the results of study 1 and study 2 clearly indicate that longer delays during the working memory task do not result in more long-term encoding due to longer maintenance periods, and consequently do not enhance episodic memory performance.

General discussion

The studies reported here extend our previous research in patients with diencephalic-hippocampal amnesia (Van Geldorp et al., 2012), with an aging study and a patient study in early Alzheimer's disease. The results of study 1 indicated that aging affects both working memory and episodic memory. Study 2 showed that patients with MCI or AD are not only impaired in episodic memory, but also in the

working memory binding task, in line with previous results showing that medial temporal lobe dysfunction results in associative working memory deficits (Della Sala et al., 2012).

It has been argued that memory problems in older adults arise from associative deficits (Chalfonte & Johnson, 1996). Naveh-Benjamin elaborated on this idea and named it the associative deficit hypothesis (2004; 2003; 2000). His studies show that older adults are selectively impaired in associative memory and not in item memory, when compared to young adults. Whereas the studies by Naveh-Benjamin focus on episodic memory only, our study also addressed associative working memory. The older adults we examined not only showed problems on our episodic memory task, but also on the working memory task. This suggests that older adults have a general binding deficit. In short, our study confirms and extends the studies by Naveh-Benjamin and colleagues.

Concerning the interaction between working memory and subsequent episodic memory, we found that delay length during the working memory task was not related to performance on the subsequent episodic memory task. In other words, longer delays during the working memory task did not facilitate long-term memory formation. This is in line with our previous study (Van Geldorp et al., 2012), in which we only examined this notion in older adults. Here were can conclude that even in young healthy adults, who may have more working memory resources than older adults, we find no evidence for the idea that medial temporal lobe involvement in working memory tasks merely reflects incidental long-term memory encoding.

Our patient study shows that patients with early stage AD experience significant difficulties with working memory binding. Our findings not only support previous studies (see for example Parra, Abrahams, Fabi, et al., 2009; Parra et al., 2011), but also corroborate results from a previous study in non-demented patients with diencephalic-hippocampal amnesia (Van Geldorp et al., 2012). Delay length affects performance of all older participants and patients, but a longer delay length does not lead to additional deficits in the patient group. This is in contrast to what we expected based on the study by Buffalo et al. (Buffalo et al., 1998). It also seems in contrast with the theory by Jeneson and colleagues (Jeneson et al., 2011, 2010; Jeneson & Squire, 2012), which states that long-term memory processes are addressed in working memory tasks when working memory capacity is exceeded, for example, when the set size is large or when the delay is long. However, longer delays did not result in larger deficits in our patients.

Despite these seemingly contrasting results, we believe that our findings can be explained within the context of exceeding working memory capacity. For example, the fact that patients are impaired irrespective of delay suggests that working memory capacity was already exceeded when the delay was short. In

addition, the task used by Buffalo et al. (1998) assessed memory for single items and not for associative information. Therefore, it could be argued that maintaining single items within working memory only relies on long-term memory processes when the delay length is long, whereas multiple items or features always requires support from long-term memory. That is, when the delay period is long, or when associations have to be maintained, working memory capacity is exceeded and long-term memory processes are required.

Working memory capacity may be exceeded in the present working memory binding task because of the associative component in the task. Long-term memory processes (requiring the medial temporal lobe) are then recruited to support performance. Also, it could also be argued that the complexity of our stimuli induces long-term memory processes. Houses and faces may be very complex stimuli, but several studies using more basic features (e.g. shapes, easily namable objects, colors or locations) found similar working memory deficits in patients with medial temporal dysfunction as well (Braun et al., 2011; Parra, Abrahams, Fabi, et al., 2009; Parra et al., 2011). This finding is in contrast with a recent neuroimaging study showing that MTL activity during a working memory task is related to long-term memory formation (Bergmann et al., 2012).

Apart from these theoretical implications, some clinical implications can be drawn as well. Working memory binding tasks could be considered useful in differentiating between healthy and pathological aging. Even in its current form, where healthy older adults showed a decline in working memory binding performance, the task reveals significant deficits in patients with MCI or AD as compared to those healthy older adults. Ideally, future research should specify a type of binding task on which healthy older adults are not impaired. One study already showed that color-color binding and shape-color binding are insensitive to healthy aging, but sensitive to AD (Parra et al., 2011). More studies are needed identify which types of binding are sensitive to pathological aging. In general, more consideration should be given to the working memory domain in patients with MCI or AD. Other components of working memory have also been implicated useful in differentiating between normal and pathological aging, such as phonological loop deficits (Belleville, Peretz, & Malenfant, 1996) and control of attention (Belleville, Chertkow, & Gauthier, 2007a).

A possible limitation of our study is that (early) Alzheimer's disease may also affect non-MTL brain areas. Although all our patients fulfilled the criteria for MCI or dementia due to Alzheimer's disease, the MTL damage in these patients is less selective than in e.g. encephalitis patients with lesions restricted to the hippocampus. Furthermore, we do not have volumetric data of the MTL in this study. Still, our well-described patient group of early Alzheimer's disease patients provides a valid model of MTL dysfunction.

Future aging studies could also shed some light on the role of attentional processes in binding. It has been suggested that older adults' episodic memory deficits resemble the deficits observed in young adults performing the task under conditions of divided attention (Castel & Craik, 2003; Craik & McDowd, 1987). However, Naveh-Benjamin already showed that divided attention causes general deficits in memory, whereas aging specifically affects binding mechanisms (Naveh-Benjamin, Hussain, et al., 2003). As his studies focus on associative processes in episodic memory rather than working memory, it would be interesting to investigate whether attention-constraining conditions affect working memory binding differently in young and older adults.

In sum, our results can be explained in light of the theory by Jeneson et al. (2011, 2010; 2012), stating that long-term memory processes are involved in working memory tasks when working memory capacity is exceeded (in this case by the associative component of the task). Working memory tasks may require support from long-term memory processes, suggesting that working memory and long-term memory are not entirely independent from each other. This is in line with neurophysiological theories on memory formation (cf. Jonides et al., 2008) that also assume a role for the MTL already at short delays. Working memory and episodic memory may (partly) be served by the same neurons, showing that the difference is more functional than structural (in anatomical sense). Future functional neuroimaging studies may provide further insight into the underlying neurocognitive mechanisms of associative working memory.

Acknowledgements

We would like to thank the following people for their contribution to data collection: Members of the Utrecht Vascular Cognitive Impairment Study Group:

- Department of Neurology, Brain Center Rudolf Magnus, UMC Utrecht: I. Verhage, I. Wielaard, K.E.R. Berendsen, B. Miltenburg, W.M. Freeze, J.E. Biessels.
- Department of Geriatrics, UMC Utrecht: H.L. Koek, J.E. de Wit, M. Versloot.

Chapter 7 Precision of working memory binding in MCI and early Alzheimer's disease

In preparation as:
Van Geldorp, B., Gorgoraptis, N., Meulenbroek, O., Husain, M., Kessels, R.P.C. Precision of working memory binding in MCI and Alzheimer's disease.

Abstract

It has been argued that the medial temporal lobe is involved in working memory tasks, specifically when task requirements exceed WM capacity. In this study, we examined working memory binding by measuring the precision with which the orientation of one to three colored bars was recalled. In addition, we measured hippocampal volume using voxel-based morphometry. Twenty patients with Mild Cognitive Impairment or dementia due to Alzheimer's disease and 28 controls performed the working memory binding task. If the medial temporal lobe is involved in working memory binding tasks because of an overload of working memory capacity, we expect that working memory precision of patients will drop dramatically with increasing set size. Results showed significantly worse working memory precision for patients, associated with their hippocampal atrophy. The notion that the medial temporal lobe is involved in working memory only when the set size is too large does not hold. Rather, we argue that the interfering effect of subsequent items may erase working memory content. In that case, healthy participants can rely on long-term memory processes, but patients with medial temporal lobe atrophy cannot.

Introduction

The medial temporal lobe (MTL) is well known for its role in long-term memory (Squire, 2009a), but its role in working memory is less clear. Recently, accrued evidence suggests that the MTL is involved in specific aspects of working memory, namely working memory binding. Binding refers to the process of integration and maintenance of visual features for a brief period of time. Both imaging and patient studies have shown that the MTL is involved in tasks that require working memory binding.

For example, neuroimaging studies show MTL activity in object-location binding (Hannula & Ranganath, 2008; D. Luck et al., 2010; Mitchell, Johnson, Raye, & D'Esposito, 2000; Piekema et al., 2006) and object-object binding (Piekema et al., 2010). Moreover, patients with MTL lesions demonstrate deficits when performing tasks using these same types of binding (Braun et al., 2011; Crane & Milner, 2005; Olson et al., 2006; Van Geldorp et al., 2012). In contrast, these patients perform normally when maintaining single features (Braun et al., 2011; Olson et al., 2006). It could thus be argued that the MTL is crucial for working memory binding.
However, MTL activity is not observed during all working memory binding tasks (Piekema et al., 2010). In addition, patients with MTL lesions perform relatively intact on some binding tasks, for example object-color binding (Braun et al., 2011). An alternative explanation could be that MTL activation is driven by working memory load, as suggested by for example Shrager et al. (2008) and Hannula et al. (2006). Consistent with this line of reasoning, Jeneson et al. (2011, 2010) state that working memory binding is impaired after MTL damage only if the capacity of working memory is exceeded and performance depends on long-term memory.

In the present study, we examined whether patients with episodic memory impairment (i.e. patients with Mild Cognitive Impairment [MCI] or early Alzheimer's dementia [AD]) show working memory binding deficits. Working memory load was varied in order to examine the theory by Jeneson et al. (2011, 2010). Most studies have tested working memory in a binary fashion, i.e., an item is either completely remembered or forgotten. As an alternative, we use a more flexible approach by measuring the variability of memory estimates around the true value (P. M. Bays, Catalao, & Husain, 2009; Paul M. Bays, Wu, & Husain, 2011; Gorgoraptis, Catalao, Bays, & Husain, 2011). In other words, we measure the precision with which sequentially presented material is recalled. Participants had to maintain the orientation of colored bars and the precision with which participants could remember the orientation was measured.

If the MTL is involved in working memory binding in general, we expect that patients show lower overall precision and more misbinding errors (i.e. incorrect binding of features belonging to different objects) than healthy controls. If the

MTL is involved in working memory binding only when the load increases beyond working memory capacity, precision will drop with increasing set size, specifically in the patient group, which would be in line with findings by Pertzov et al. (2013). We also examined patients' MRI scans and measured hippocampal volume using volumetric analyses. It is hypothesized that hippocampal volume will correlate with working memory precision, specifically with increasing set size. Also in line with the predictions from Pertzov et al. (2013), we expect that the medial temporal lobe is involved in any item in the sequence, except the last one, which is still under the focus of attention.

Materials and methods

Participants

A total of 20 patients and 28 healthy controls participated in this study. All patients were diagnosed with either MCI (either single or multiple domain; according to the criteria by Petersen et al., 2001) or dementia due to Alzheimer's disease (according to the criteria by McKhann et al., 2011). Diagnoses were made using a multidisciplinary approach, supported by neuroradiological, neuropsychological and medical examination. All MRI scans showed clear medial temporal atrophy and/or cortical atrophy. All participants provided informed consent. The study conforms to the Declaration of Helsinki. Since no differences in working memory precision were observed when patients with MCI and Alzheimer's dementia were compared ($t(18)=0.87$, $p=.40$), we collapsed these groups into one patient group.

Demographics for both groups are displayed in Table 1. Note that patients' performance is comparable to controls on a standard neuropsychological working memory span task (digit span). The groups were matched for age and education (assessed using the seven categories from Verhage 1964). The distribution of men and women in the two groups differed marginally ($\chi^2(1)=3.19$, $p=.07$). However, sex did not influence working memory precision ($t(46)=1.03$, $p=.31$). Therefore, sex was not included as a covariate in the analyses.

Paradigm

The paradigm is based on a previous study in healthy participants (see experiment 1 in Gorgoraptis et al., 2011). It is a computerized working memory precision task, in which participants were presented with a sequence of one to three colored bars (see Figure 1). The bars differed in color and orientation and were presented for 500 ms each at the centre of the display, followed by a blank screen for 500 ms. The colors of the items in each trial were randomly chosen from five easily distinguishable colors. The orientation of each item was random, but the orientation of items in each sequence differed by at least10°.

Table 1 Demographical and Clinical Characteristics for all Participants

	Patient group	Control group	Statistic, *p*
N	20	28	
Sex (M/F)	10/10	21/7	$\chi^2(1)=3.19$, p=.07
Age (mean, SD)	73.40 (7.19)	74.00 (6.70)	F(1,46)<1, n.s.
Education[a] (mode, range)	6 (3-7)	5 (2-7)	Mann-Whitney U=238, p=.37
MMSE (mean, range)	25.75 (21-29)	28.57 (25-30)	F(1,46)=31.74, p<.001
WAIS-III Digit span[b] (mean, SD)	13.80 (3.37)	14.61 (4.33)	F(1,46)<1, n.s.
Word list learning[c] total 1-5	28.30 (11.11)	-	
Word list learning delayed recall	3.20 (3.82)	-	
Word list learning recognition	21.85 (4.90)	-	
TMT-A[d], seconds	59.65 (23.12)	-	
TMT-B, seconds	175.60 (119.88)	-	

[a] Assessed using the seven categories from Verhage (1964)
[b] Wechsler Adult Intelligence Scale – Third Edition (D. Wechsler, 1997)
[c] Word list learning: Rey Auditory Verbal Learning test (Van der Elst et al., 2005)
[d] Trail Making Test (Reitan, 1985)

The probe was displayed within a circle to make it stand out from the to-be-remembered items and consisted of a bar of the same color as one of the studied items, but with a random orientation. In other words, color served as a cue for the target item. The participant then had to use a response dial (Logitec) to rotate the probe until it matched the orientation of the remembered target item. At the start of each trial, participants were not aware of the amount of items they were to remember.

All participants completed 90 trials, presented in nine blocks of ten trials. There are six possible combinations of set size (1-3) and serial position of the target within the sequence. For each combination, there were 15 trials, resulting in a total of 90 trials. Administration of the task lasted approximately 15 to 20 minutes.

Analysis

Behavioral data. We measured the deviation in degrees between the original orientation of the target item and the orientation as reported by the participant. Precision is then calculated as the reciprocal of the SD of error across trials (for details on the analysis methods see P. M. Bays et al., 2009; Gorgoraptis et al., 2011).

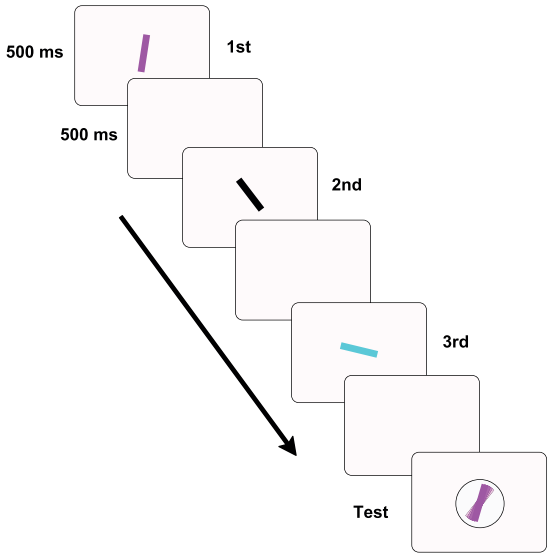

Figure 1 Schematic overview of the task. Participants were presented with a sequence of colored bars, of which both color and orientation had to be maintained. In each trial, set size varied between one and three items. At test, color was probed and participants had to adjust the orientation of the probe item so that it matched the orientation of the original item (in this case, the first).

To examine the effect of set size on precision, we performed a 2 (group: patients vs. controls) by 3 (set size: 1, 2 or 3) repeated measures ANOVA. Since Mauchly's test showed that the assumption of sphericity was violated, we corrected the degrees of freedom, using the Greenhouse-Geisser correction.

In order to examine the effect of serial position of the target, we used the 3-item trials only for a 2 (group: patients vs. controls) by 3 (serial position: 1, 2 or 3, with 1 being the last item) repeated measures ANOVA.

Source error modeling. We used a probabilistic model in order to quantify the contribution of three different sources of error to working memory precision. This method has previously been described by Bays et al. (2009) and Gorgoraptis et al. (2011). This model attributes errors to Gaussian variability in memory for the orientation of the target, the probability of misreporting the orientation of a non-target in the sequence, and the probability of responding with a random orientation. For this modeling process, data for each participant had to be divided between a large number of conditions. In order to solve this problem, we pooled across participants to maximize the available data.

Neuroimaging data. High-resolution structural MR images were available for all patients. They were acquired with a T1-weighted MP-RAGE sequence with an isotropic voxel size (1x1x1 mm). The hippocampus was automatically segmented using FSL4.1 FIRST v1.1 (Analysis Group, FMRIB, Oxford, UK; S. M. Smith et al., 2004; Woolrich et al., 2009). This method is based on Bayesian statistical models of shape and appearance for subcortical structures from 317 manually labeled T1-weighted MR images. To fit the models, the probability of the shape given the observed intensities is used (Patenaude, 2007). After segmentation, volumes were calculated using a script in Matlab7.2 (MathWorks; Natick, MA, USA). Only boundary corrected data were used. Visual inspection of the segmented structures projected onto the T1-weighted MRI scans was done using MRIcroN Beta 7 (www.mricro.com/mricron), to check if the segmented structures align with the same structures on the T1. Absolute total hippocampal volumes were transferred to SPSS 15.0 for Windows (Lead Technologies Inc. SPSS Inc., Chicago, Illinois, USA) and subjected to a partial correlation (one-tailed) with working memory precision. There was no significant difference between right and left hippocampal volume ($t(19)=0.06$, n.s.). We believe that the results of the correlation analyses are more robust when using total hippocampal volume.

In order to examine the relationship between precision over the three set sizes and hippocampal volume, while controlling for global atrophy, we performed a repeated measures ANCOVA with a within-subject factor of three levels (set size: 1, 2 or 3) and two covariates (hippocampal volume and Brain Parenchymal Fraction). Brain Parenchymal Fraction (BPF: (gray matter + white matter)/ intracranial volume; Juengling & Kassubek, 2003) is a measure of global brain atrophy, and is included in the model as a regressor of no interest. To determine gray matter, white matter and cerebrospinal fluid volume for calculation of BPF, the structural MR images were segmented into gray matter, white matter, and cerebrospinal fluid with the Voxel Based Morphometry (VBM) toolbox in SPM using priors (default settings). A similar repeated measures ANCOVA was performed to examine the relation between precision over different target positions and hippocampal volume. That is, a repeated measures ANCOVA with three within-subject levels (serial position: first, second and last item) and two covariates (hippocampal volume and BPF).

Results

Behavioral data. Precision was significantly above chance level for both groups on all conditions (all p-values <.001). The 2 (group) by 3 (set size) repeated measures ANOVA revealed a main effect of set size ($F(1.57, 72.15)=30.78$, $p<.001$), see Figure 2a.

Pairwise comparisons showed that precision decreases significantly with increasing set size: set size three is significantly worse than set size two (p<.001) and set size two is significantly worse than set size one (p<.001). A significant main effect of group was observed (F(1,46)=4.14, p=.05). An independent samples t-test showed that patients performed significantly worse than controls on trials with two or three items (t(46)=-2.24, p=.03, and t(46)=-2.19, p=.03, respectively). No interaction between set size and group was found (F(1.57, 72.15)<1, n.s.).

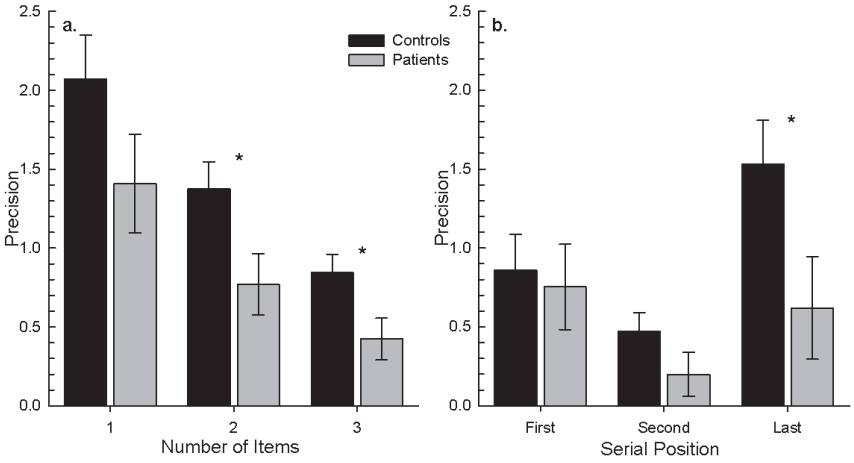

Figure 2 **a.** Working memory precision. Precision is modulated by set size. Patients performed worse than controls, reflected in significant differences on trials with two or three items. **b.** Serial position. Precision is modulated by the position of the target item. Controls show a clear effect of recency, whereas patients show a much weaker recency effect.

The 2 (group) by 3 (serial position) repeated measures ANOVA revealed an effect of serial position (F(1.68, 77.31)=6.51, p=.004), see Figure 2b. Pairwise comparisons showed that controls' performance on the last was item significantly better than on the second (t(27)=3.98, p<.001) and marginally better than on the first item (t(27)=1.90, p=.07). Patients performed only marginally better on the last item than on the second item (t(19)=2.02, p=.06), but not the first item (t(19)=-0.42, n.s.). The main effect of group was marginally significant (F(1,46)=3.34, p=.07). This effect was due to a significant group difference on the last item only (t(44.19)=-2.33, p=.02). No interaction between serial order and group was observed (F(1.68, 77.31)=2.09, n.s.).

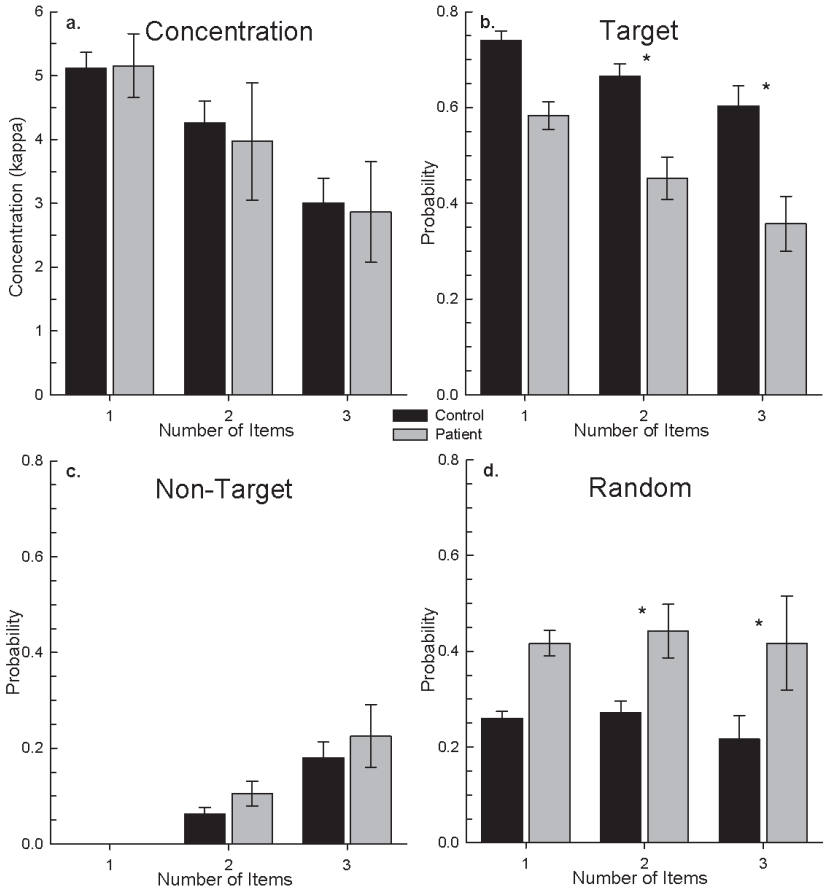

Figure 3 **a.** Concentration of responses decreased with increasing set size, indicating that variability in responses increased. **b.** The probability of responding to the target orientation decreased with increasing set size. There is a significant difference between the patient group and the control group. **c.** The probability of responses to the non-target orientation increased with increasing set size, but there is no significant group difference. **d.** The probability of responses in a random orientation is stable over an increasing set size, but there is a significant group difference.

Source error modeling. For the concentration of responses around the target orientation, no significant differences between patients and controls are observed (two item trials: χ^2=0.07, p=.39; three item trials: χ^2=0.39, p=.53), see Figure 3a. We do find that patients are significantly less likely to respond to target item orientation (two item trials: χ^2=8.68, p=.003; three item trials: χ^2=10.56, p=.001), see Figure 3b. The

probability of responding to a non-target orientation (see Figure 3c) does not result in any group differences (two item trials: χ^2=1.44, p=.23; three item trials: χ^2=0.197, p=.66). Patients respond with a random orientation more often than controls (two item trials: χ^2=4.05, p=.044; three item trials: χ^2=6.34, p=.012), see Figure 3d.

Neuroimaging data. Segmentation and volumetric analyses showed an average (left plus right) hippocampal volume of 6.20 mm^3 (SD=1.03). The partial correlation analysis showed a significant correlation (r=.46, p=.03) between hippocampal volume and precision. Since Mauchly's test showed that the assumption of sphericity was violated, we corrected the degrees of freedom, using the Greenhouse-Geisser correction. The repeated measures ANCOVA showed no significant main effect of set size (F(1.18, 18.94)=1.87, p=.19). The interaction between set size and hippocampal volume was found to be significant (F(1.18, 18.94)=4.39, p=.04). When examining the parameter estimates of the different set sizes, we observed a significant correlation between hippocampal volume and precision on set size one (β=.72, p=.03), a marginally significant correlation between hippocampal volume and precision on set size two (β=.28, p=.06), but a non-significant correlation between hippocampal volume and precision on set size three (β=.13, p=.23). Focusing on the serial position of the target, we found no significant main effect of serial position (F(2,32)=1.90, p=.17) and no significant interaction effect between hippocampal volume and serial position (F(2,32)=1.14, p=.33).

Discussion

In the present study, we measured working memory precision in patients with MCI or early Alzheimer's dementia. Summarizing the results, patients show an overall impairment in working memory precision, mainly driven by impaired performance on trials with two or three items. Precision decreases with increasing set size, but this effect is not more pronounced in patients than in controls. Patients are less likely to respond to target item orientation, but do show more random responses. Looking at serial position in more detail, we observed an intact primacy effect, but a diminished recency effect in the patient group. Volumetric analyses showed that hippocampal volume correlates with overall precision, specifically in trials with one or two items.

The fact that working memory precision is lower in the patient group and correlates with hippocampal volume suggests that the MTL is involved in this working memory binding task. This is in line with previous findings indicating that the MTL is involved in relational memory (Konkel & Cohen, 2009), not only in long-term memory but also in working memory (Hannula & Ranganath, 2008; e.g.,

Mitchell, Johnson, Raye, & D'Esposito, 2000; Olson et al., 2006; Van Geldorp et al., 2012). In contrast, working memory for single items (i.e. digit span) was not impaired in our patients. In recent years, several explanations have been put forward on the nature of this involvement.

The first explanation by Jeneson and colleagues (2011, 2010; 2012) states that the MTL is only involved when the material exceeds the capacity of immediate memory, which is for example the case when the set size is too large. When working memory capacity is exceeded, long-term encoding is required (relying on the hippocampal memory system), as a result of which patients with MTL damage start failing the task. This is supported by a recent fMRI-study, showing that associative working memory drives MTL activity only for associations remembered in de long term (Bergmann et al., 2012). Our results seem to be in line with Jeneson's explanation, showing that the impairment in patients is mainly apparent in trials with two and three items. However, we would then also have expected the largest set size (3 items) to correlate most strongly with hippocampal volume, which was not the case. In fact, the interaction effect between hippocampal volume and set size suggests that the hippocampus becomes *less* important for working memory precision with increasing set size.

The theory by Jeneson (2011, 2010; 2012) could possibly explain why controls, similar to young adults (Gorgoraptis et al., 2011), showed a strong recency effect on this task, whereas patients show a much weaker recency effect. When the last item of the sequence is added, working memory capacity is exceeded and performance relies on long-term memory processes. That may explain why precision for specifically recent items is affected by hippocampal atrophy. However, volumetric analyses revealed that precision on the different serial positions was not related to hippocampal volume or BPF.

Another hypothesis following the theory by Jeneson (2011, 2010; 2012) is that the patients' impairment should increase with increasing set size. However, we did not find such an interaction effect between group and set size. In other words, patients' working memory precision did not disproportionately decrease with increasing set size. In summary, there are several reasons why we believe that our data does not fit the hypothesis that the MTL is involved only in working memory conditions with high memory load.

The second explanation focuses on the working memory capacity limit of three or four items (S. J. Luck & Vogel, 1997). This model would predict optimal performance until the capacity limit is reached and a sudden drop in performance after that point, much like Jeneson and Squire (2012) show in their review. Our participants (like the young adults in Gorgoraptis et al., 2011) showed a gradual decrease in precision as the set size increased. Even with larger set sizes (up to five items), young adults did not show a sudden drop in performance (Gorgoraptis et

al., 2011). According to this view, we would also expect a sudden increase in responses with a random orientation when the set size increases. However, this is not what we found.

Finally, a more likely view is that subsequent items are interfering with working memory content. This explains why precision on one-item trials is not significantly impaired. When subsequent information interferes, one would expect misbinding errors. This is precisely what we found. Gorgoraptis et al. (2011) compared sequential presentation with simultaneous presentation and showed that precision is lower when items are presented sequentially instead of simultaneously. This is due to interfering effects of subsequent items rather than mere time decay or spatial overwriting. Interference of subsequent items may have erased working memory content. When this happens, controls successfully rely on their intact long-term memory to avoid interfering effects from subsequent items, whereas patients cannot.

In conclusion, we argue that this working memory binding task relies at least in part on the MTL. There remains some discussion as to which mechanisms underlie the impairments that our patients with MCI and Alzheimer´s dementia show. The argument that the MTL is involved when working memory load is increased does not hold, because we would then expect a decrement with increasing set size that is stronger for patients than for controls. In addition, when adding more items, we found no sudden drop in precision. Therefore, the capacity of working memory may not be hippocampally mediated, but may rather rely on the fronto-parietal working memory network. Instead, we argue that not the number of items as such, but the serial position of the items is crucial. Rather than an effect of exceeding working memory capacity, our findings strongly suggest an interfering effect of subsequent items with the contents of working memory. Also, our findings stress that working memory function, in addition to episodic memory, should be studied in more detail in patients with MCI or Alzheimer's dementia in order to shed light on the hippocampal involvement in working memory.

Chapter 8 Cognitive and neuro-psychological underpinnings of relational and conjunctive working memory binding across age

Submitted as:
Van Geldorp, B., Parra, M.A., Della Sala, S., Kessels, R.P.C. Cognitive and neuropsychological underpinnings of relational and conjunctive working memory binding across age.

Abstract

The ability to form associations (i.e. binding) is critical for memory formation. Recent studies suggest that aging specifically affects relational binding (associating separate features), but not conjunctive binding (integrating features within an object). Possibly, this dissociation may be driven by the spatial nature of the studies so far. Alternatively, relational binding may simply require more attentional resources. We assessed relational and conjunctive binding in three age groups and we included an interfering task (that is, an articulatory suppression task).

Binding was examined in a working memory (WM) task using non-spatial features: shape and colour. Thirty-one young adults (mean age 22.35), 30 middle-aged adults (mean age 54.80) and 30 older adults (mean age 70.27) performed the task.

Results show an effect of type of binding and an effect of age, but no interaction between type of binding and age. The interaction between type of binding and interference was significant.

These results indicate that aging affects relational binding and conjunctive binding similarly. However, relational binding is more susceptible to interference than conjunctive binding, which suggests that relational binding may require more attentional resources. We suggest that a general decline in WM resources associated with frontal dysfunction underlies age-related deficits in WM binding.

Introduction

To accurately represent the external world in memory one needs to keep in mind the links between features comprised within complex stimuli (e.g., shape, colour, size, orientation, etc.) and between the stimuli scattered in the experienced scene (e.g., objects and their locations, relation between objects, etc.). At least two types of binding functions appear to support memory for such links. One type, namely conjunctive binding (i.e. integrating features within object representations), can support the former links. The other type, known as relational binding, supports the latter (Mayes et al., 2007; Moses & Ryan, 2006).

Recent studies have documented a dissociation of these binding functions in short-term or working memory (Parra et al., 2013; WM; e.g., Piekema et al., 2010). These distinctions are proving relevant to the study of these functions in healthy aging. Age appears to impact on relational binding functions quite broadly (Old & Naveh-Benjamin, 2008). Accrued evidence suggests that the ability to process relational bindings in WM declines with age. For example, Mitchell et al. (2000) showed that older adults performed significantly worse than younger adults when an object and its location had to be maintained together. In addition, older adults show worse performance when maintaining face-face or face-location associations relative to younger participants, whereas no differences were found on item memory (Bastin & Van der Linden, 2006).

In contrast, conjunctive binding seems to be insensitive to the effects of age (Brockmole & Logie, 2013; Brockmole, Parra, Della Sala, & Logie, 2008; Brown & Brockmole, 2010; Parra, Abrahams, Logie, & Della Sala, 2009). Although maintaining two colours that are bound in a conjunctive fashion results in worse performance than maintaining unicoloured objects or two non-conjunctive colours, older adults are not differentially affected than younger adults. Thus, age does not seem to have an effect on conjunctive binding, even though older adults do seem to have a smaller working memory capacity (Brockmole & Logie, 2013; Brockmole et al., 2008; Jost, Bryck, Vogel, & Mayr, 2011).

The finding that relational binding does decline with age whereas conjunctive binding does not, may be explained by the role of the hippocampus in binding. Several neuroimaging studies assessing relational binding found activation in the hippocampus (Mitchell, Johnson, Raye, & D'Esposito, 2000; Piekema et al., 2006) and related medial temporal lobe structures (Hannula & Ranganath, 2008; D. Luck et al., 2010). Such activation is not observed in conjunctive binding or in working memory for single objects or locations (Piekema et al., 2006, 2010).

In addition, lesion studies report deficits in relational binding in patients with damage in the hippocampus and related medial temporal lobe structures (Braun et al., 2011; Crane & Milner, 2005; Konkel, Warren, Duff, Tranel, & Cohen, 2008;

Olson et al., 2006; Parra et al., 2013; Van Geldorp, Bouman, Hendriks, & Kessels, 2014b). Conjunctive binding seems to render no deficits (Baddeley, Allen, & Vargha-Khadem, 2010; Baddeley, Jarrold, & Vargha-Khadem, 2011; Braun et al., 2011; Parra et al., 2013; Van Geldorp et al., 2014b), just like working memory for single items or features (Braun et al., 2011; Konkel et al., 2008; Olson et al., 2006). Furthermore, Jon, a patient with a 50% reduction of hippocampal volume described by Baddeley et al. (2010), does not show any problems with conjunctive binding or context-free semantic memories, but he does have problems with context-rich episodic memory (VarghaKhadem et al., 1997).

It is known that the medial temporal lobes and specifically the hippocampus shrink with increasing age (Du et al., 2006; Raz, Rodrigue, Head, Kennedy, & Acker, 2004). Accordingly, it can be suggested that the age-related decline in relational binding performance may be attributed to age-related hippocampal atrophy. However, a feature of the abovementioned aging studies which prevents upholding the claim about a general relational binding impairment in older adults is that in most of these studies, object-location binding was the function assessed. The hippocampus is known to be involved in spatial processes and older adults have deficits in feature memory for location (and not for item or colour; Chalfonte & Johnson, 1996). Spatial processing impairment and not relational binding impairment may therefore explain the pattern of performance observed in older adults.

An additional limitation is that most studies do not directly compare relational and conjunctive binding. The studies that did investigate the role of the hippocampus by directly comparing relational and conjunctive binding (Braun et al., 2011; Piekema et al., 2006, 2010; Van Geldorp et al., 2014b) did not use the same type of information for both types of binding. However, they seem to confirm the notion that relational (i.e., object-location) binding involves hippocampal activation and conjunctive (i.e., object-colour) binding does not (Piekema et al., 2006, 2010). Nevertheless, the spatial component in those studies prevents any strong conclusions.

Another explanation for the finding that relational binding declines with age but conjunctive binding does not, relates to attentional processes. In conjunctive binding, the stimulus may be perceived as one object (i.e., feature integration takes place), implying that conjunctions may be processed automatically without attention (Allen et al., 2012; Kubovy et al., 1999). Indeed, conjunctive binding deficits neither emerge nor are exacerbated under conditions of high attentional load (Brown & Brockmole, 2010). In contrast, relational binding may be more resource-demanding, as demonstrated by the finding that a concurrent task hampered verbal-spatial binding (Elsley & Parmentier, 2009). In the only study (to our knowledge) that directly compared relational and conjunctive binding using

the same features (i.e. colour and shape), it is argued that conjunctions are processed automatically, whereas relational bindings are more resource demanding (Ecker, Maybery, & Zimmer, 2013).

Mitchell et al. (2000; 2006) argue that binding relies on a frontal-hippocampal circuit, in which prefrontal reflective working memory processes create opportunities for the hippocampus to form feature bindings. This is in agreement with a more recent suggestion by Sander and colleagues (2012), who also distinguish frontal top-down processes and mediotemporal binding processes. Therefore, decreased frontal or attentional functions, rather than decreased hippocampal functioning, may underlie the binding deficits observed (Brickman et al., 2006; Salthouse, 1990; Sander et al., 2012; W. D. Spencer & Raz, 1995).

We attempted to take the abovementioned issues into account by designing a task that examines both relational and conjunctive binding using the same type and amount of information. For both types of binding, we used non-spatial features, namely shape and colour. Participants had to bind four shapes and four colours in either a relational or a conjunctive fashion. The task permits the comparison of relational and conjunctive processes using a within-subjects design. The task was administered in three age groups to examine the effect of aging. If relational binding simply requires more resources, then relational binding should be more sensitive to an interfering task than conjunctive binding.

If the age-related dissociation of relational and conjunctive binding is driven by a deficit only in holding the link between pairs of items, independent of the nature of the to be bound information (i.e., whether or not spatial information is relevant to the task), our non-spatial binding tasks should confirm such a dissociation. More specifically, we predict that if such an age-related decline reflects a hypo-functional hippocampus in the old, we should observe age-related relational decline during both a non-interference and an interference task. Alternatively, if such an age-related decline arises primarily form defective reflective processes which are known to require attentional control, only the interference task should lead to an effect of age.

Methods

Participants

A total of 91 healthy volunteers participated, divided into three age groups: 31 young adults (mean age 22.35 SD = 3.21, 19 females), 30 middle-aged adults (mean age 54.80 SD = 5.04, mean MMSE: 29.63 range 28-30, 16 females) and 30 older adults (mean age 70.27, SD = 3.31, mean MMSE: 29.03,_range 27-30, 19 females). For descriptive information of the participants, see also table 1. Five additional

Table 1 Participant characteristics and performance on standard neuropsychological tests

	Young adults	Middle-aged (50+)	Older adults (60+)	Statistics, *p*	Specification
N	31	30	30		
Age (Mean, SD)	22.35 (3.21)	54.80 (5.04)	70.27 (3.31)		
Sex (M/F)	12/19	14/16	11/19	χ^2 (2)=0.70, n.s.	
Education level (Mode, range)[a]	6 (4-7)	6 (4-7)	6 (2-7)	χ^2 (2)=6.92, p=.03	Old=Middle<Young
NART IQ (Mean, SD)	95.00 (10.75)	103.63 (12.04)	108.90 (17.80)	F (2,88)=7.86, p=.001	Old=Middle>Young
Intellectual ability (Mean, SD)[b]	-0.06 (0.69)	-.02 (0.66)	0.08 (1.12)	F (2,88)=0.19, n.s.	
MMSE (Mean, SD)	-	29.63 (0.62)	29.03 (1.07)	F (1,58)=7.13, p=.01	Old<Middle
Working memory					
WAIS-III Digit Span	16.10 (2.97)	16.00 (2.84)	14.33 (3.34)	F(2,88)=3.18, p=.05	Old<Young
Corsi Block tapping	19.58 (2.41)	16.93 (3.05)	14.80 (2.27)	F(2,83)=23.51,p<.001	Old<Middle<Young
Executive function					
Trail making test					
TMT-A (seconds, SD)	20.39 (6.43)	32.60 (12.67)	44.27 (20.15)	F(2,88)=21.66, p<.001	Old>Middle>Young
TMT-B (seconds, SD)	43.77 (13.98)	64.00 (22.56)	99.67 (49.30)	F(2,88)=23.52, p<.001	Old>Middle>Young
TMT-B minus TMT-A	23.39 (9.52)	31.40 (13.41)	55.40 (39.08)	F(2,88)=14.18, p<.001	Old>Middle=Young
Letter Fluency	40.97 (10.07)	38.83 (8.12)	36.48 (11.56)	F(2,87)=1.51, n.s.	
Long-term memory					
Location Learning test					
Total displacement	9.16 (9.22)	18.23 (18.04)	24.64 (16.59)	F(2,83)=7.60, p=.001	Old=Middle<Young
Learning index	0.87 (0.20)	0.80 (0.49)	0.54 (0.28)	F(2,83)=6.46, p=.002	Old<Middle=Young
Recall score	-0.77 (1.61)	-0.33 (0.96)	-1.08 (1.94)	F(2,83)=1.67, n.s.	

[a] Educational level is assessed using the seven categories from Verhage (1964).

[b] Intellectual ability is the combined z-score of NART IQ and Education level, see methods section for more details.

participants were tested but excluded. In two cases (one young adult and one middle-aged adult), a software error precluded complete administration of the task. Two participants were excluded because of psychiatric diseases treated with psychoactive medication (one middle-aged adult, and one young adult). One older adult was excluded because she performed at least one standard deviation below normative data on all neuropsychological tests and also performed below chance level in three out of four task conditions.

No significant group differences were found with respect to sex distribution: χ^2 (2, N=91) = 0.70, p = .71. We registered education level and estimated IQ as measured by the Dutch version of the NART (Schmand et al., 1991). However, these variables in isolation may not be perfectly suitable for matching purposes. That is, education level does not reliably reflect intellectual abilities in the elderly group, as specifically the elderly women did not always have access to higher education fitting their abilities. In turn, the NART is a verbal measure of IQ, measuring semantic abilities that even increase with age (Uttl, 2002). Therefore, it can be expected that in the middle-aged and older groups, education estimates are too low and IQ estimates too high as compared to young adults. In order to control for this problem, we calculated z-values and combined the two measures into one averaged z-score, named intellectual ability. Groups did not significantly differ on this measure (F (2, 88) < 1, n.s.).

Task

All participants performed a computerized working memory binding task (see figure 1). The task consisted of four blocks of twenty trials each. The order of blocks was counterbalanced between participants.

In each trial, four coloured shapes made of shapes and colours that are difficult to verbalize (in order to minimize long-term memory involvement, see Parra, Abrahams, Logie, & Della Sala, 2010) were presented simultaneously for four seconds. Subsequently, after a retention interval of one second, a test screen presented one set of five shapes and one set of five colours. The participants were asked to reconstruct the four coloured shapes seen before by first clicking on the colour and then clicking on the corresponding shape. The distracter shape and colour were added to reduce the probability to answer correctly by guessing. Each condition consisted of twenty trials containing four stimuli, resulting in a total of 80 to be remembered combinations in each condition. Chance level was determined to be 16%, corresponding to 12.8 correctly bound items per condition as a result of guessing.

The shapes and colours were presented either as conjunctions of features or as relations of features. In the conjunctive binding condition, the colour fills in the

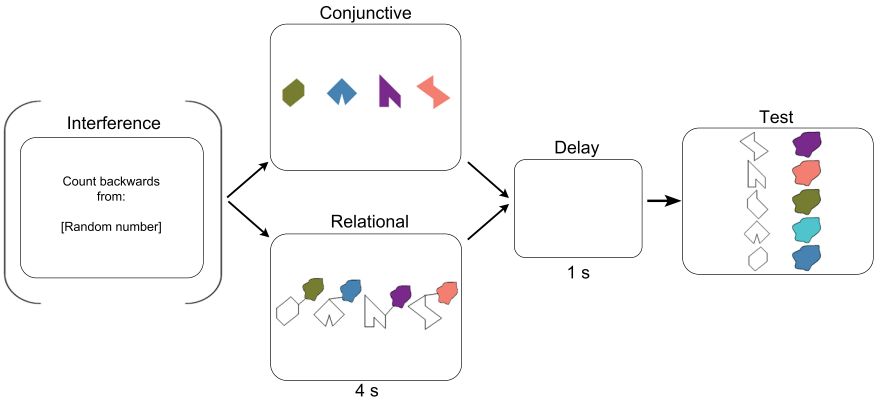

Figure 1 Schematic overview of the working memory binding task. There are two binding conditions (conjunctive and relational) and both have one condition with and one without interference. The interfering task is an articulatory suppression task, in which participants have to count backwards during encoding and maintenance. In the test phase, participants have to reconstruct the four stimuli.

shape. In the relational binding condition, the colour was paired with the shape. Each binding condition was performed with and without interference. The interfering task consisted of an articulatory suppression task in which participants had to count backwards in ones from a random number while encoding and maintaining the stimuli. This led to a 2 (condition: relational vs. conjunctive) x 2 (task: with and without interference) x 3 (group: young, middle aged and older adults) design. The four conditions are: conjunctive binding with interference, relational binding with interference, conjunctive binding without interference and relational binding without interference.

Procedure

All participants provided written informed consent. The MMSE was used only for the middle-aged and older adults to screen for severe cognitive deficits. We assessed working memory using a verbal and a visuospatial working memory task, respectively the WAIS-III Digit Span subtest (D. Wechsler, 1997) and the Corsi block tapping task (Kessels, van Zandvoort, Postma, Kappelle, & de Haan, 2000). Measures of executive functioning are the Trail Making Test (Reitan, 1985) and Letter Fluency (Lezak, 2004). Long-term memory was assessed using the Location Learning Test (Kessels, Nys, Brands, Van den Berg, & Van Zandvoort, 2006).

Analyses

The number of correct bindings in each condition was measured. Group is the independent variable used as a between-subject factor. Binding type (relational, conjunctive) and interference (interference, no interference) are within-subject factors. Performance on the different conditions is used as a dependent variable. We performed a 2 (binding) x 2 (interference) repeated measures ANOVA to investigate the effects.

In order to assess whether performance on the neuropsychological tests could predict working memory binding task performance, we used hierarchical multiple regression analyses. Task performance on the four conditions was transformed into z-scores and averaged, in order to obtain one score for task performance. This score was entered into the model as a dependent. We are interested in whether the tests that are assumed to rely on 'frontal function' (Digit Span, Corsi block tapping, Trail Making Test and Fluency) or the test scores that are assumed to rely on 'hippocampal function' (Location Learning Test) can more reliably predict task performance. In the first regression analysis, we entered the frontal test scores first and then added the hippocampal test scores to the model. In the second regression, we entered the hippocampal test scores first and then added the frontal test scores.

Results

Performance on the standard neuropsychological tests is summarized in table 1. As could be expected, the older adults show significant deficits in measures of working memory, long-term memory and executive function as compared to the middle-aged adults and young adults.

The results of the working memory binding task (see figure 2) reveal a significant effect of age group F (2, 88) = 14.72, p < .001. Young adults performed better than both middle-aged (p = .001) and older adults (p < .001). The difference between middle-aged adults and older adults was not significant (p = .36). Performance on the relational binding condition was significantly worse than on the conjunctive binding condition (F (1, 88) = 16.48, p < .001). The interference condition resulted in significantly worse performance relative to the non-interference condition (F (1, 88) = 68.18, p < .001). The interaction between interference and binding type was significant (F (1, 88) = 4.71, p = .03). An interfering task hampers the overall performance, but the interference effect is stronger in the relational binding condition. No additional interaction effects were statistically significant (all p-values >.1).

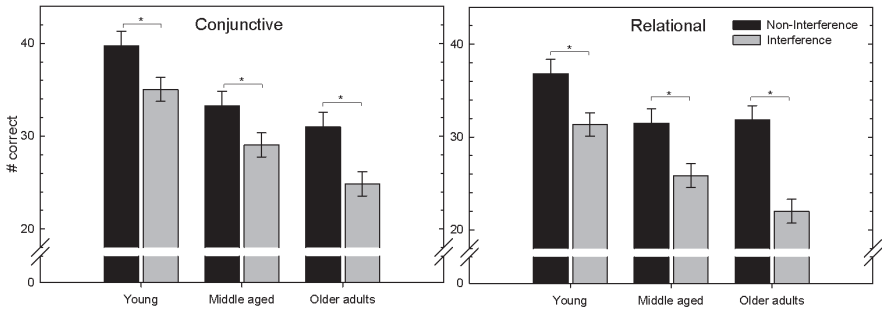

Figure 2 Results for conjunctive binding (left) and relational binding (right). See text for detailed description of results. * significant, $p<.05$.

Figure 2 also shows that when young adults are subjected to an interfering task, their relational binding performance drops to the level of older adults (t (59) = -0.24, p = .81). Conjunctive binding performance of young adults in the interference condition is well above the performance level of older adults (t (59) = 1.98, p = .05). The first regression analysis, in which we first entered the frontal test scores and then added the hippocampal test scores, shows that young adults' task performance is not reliably predicted by frontal test scores (R^2 = .29, F (5, 25) = 2.02, p = .11). Adding the hippocampal test scores to the model did not significantly change this (R^2 = .41, F_{change} (3, 22) = 1.55, p = .23). For the middle-aged adults, 48% of their task performance is explained by the frontal test scores (R^2 = .48, F (5, 25) = 4.35, p = .01). The predictors that make a significant contribution to the model are Digit Span (β = .52, t (24) = 2.70, p = .01) and Trail Making Test (B minus A; β = -.44, t (24)= -2.50, p = .02). Adding the hippocampal test scores to the model did not significantly change the outcomes (R^2 = .52, F_{change} (3, 21) = 0.62, p = .61). For the older adults, 51% of their task performance is explained by the frontal test scores (R^2 = .51, F (5, 19) = 3.90, p = .01). However, none of the predictors on its own contributed significantly to the model. Adding the hippocampal test scores to the model did not significantly change the outcomes (R^2 = .54, F_{change} (3, 16) = 0.40, p = .76).

The second regression analysis, in which we first entered the hippocampal test scores and then added the frontal test scores, reveals a different pattern of results. For the young adults, 28% of their performance is explained by the hippocampal test scores (R^2 = .28, F (3, 27) = 3.41, p = .03). However, none of the predictors on its own provided a significant contribution to the model. Adding the frontal test scores to the model did not significantly change the outcomes (R^2 = .41, F_{change} (3, 22) = 1.55, p = .23). Middle-aged adults' performance was not reliably explained by the hippocampal test scores (R^2 = .18, F (3, 26) = 1.93, p = .15). Adding the frontal test scores to the model significantly increased the amount of variance explained by

the model (R^2 = .52, F_{change}(5, 21) = 2.93, p = .04). The predictors that make a significant contribution to the model are Location Learning test (learning index; β = -.44, t (21) = 2.50, p = .02), Trail Making Test (part A; β = .68, t(21) = 2.49, p = .02) and Corsi block tapping (β = -.59, t (21) = -2.32, p = .03). Older adults' performance was not reliably explained by the hippocampal test scores (R^2 = .14, F (3, 21) = 1.18, p = .34). The change in the amount of variance that can be explained by adding the frontal test scores to the model was marginally significant (R^2 = .54, F_{change}(5, 16) = 2.77, p = .06). However, none of the predictors on its own provided a significant contribution to the model.

Discussion

In the present study, we attempted to clarify whether aging influences relational binding more than conjunctive binding. We eliminated the spatial component from the binding task, which could possibly explain the previously observed age-related relational binding decline through hippocampal involvement. In order to examine the effect of frontal reflective or attentional processes, we added an interference task. The results show an overall decrease in task performance with increasing age. However, relational binding was not disproportionately affected by aging. Additionally, interference hampered the performance and this effect was larger for relational binding as compared to conjunctive binding, regardless of age.

Aging was found to present with a decrease in performance on standard neuropsychological measures of working memory in this sample of cognitively unimpaired older people compared to the young adults (all MMSE scores are above 27). Interestingly, the working memory binding task showed that aging affected both types of binding similarly. Together, these two findings suggest a general decline in working memory rather than a specific decline in relational binding. This is in contrast with our hypothesis and previous research showing that conjunctive binding is not susceptible to the effects of normal aging (Parra, Abrahams, Logie, et al., 2009). In line with our results, other studies showed that aging affects different types of binding to the same extent (Bastin & Van der Linden, 2006; Hanaki et al., 2011). However, those studies investigated different types of relational binding and did not contrast relational and conjunctive binding. That is, Bastin and Van der Linden (2006) used face-face and face-location associations and Hanaki et al. (2011) used object-location and object-colour associations. Object-colour binding was in that study examined by presenting objects with a surrounding coloured square. It can be debated whether this is a form of conjunctive or relational binding, as it can be questioned whether this results in a unified representation.

An important strength of our study is the fact that both types of binding were assessed using the same type of information. In the absence of a spatial component that was often present when examining relational binding in previous studies, we did not find evidence that relational binding is more affected by aging than conjunctive binding. The medial temporal lobe may have been involved in relational binding tasks because the hippocampus is involved in memorizing spatial information (Parra et al., 2013; Stepankova, Fenton, Pastalkova, Kalina, & Bohbot, 2004). Although the current study does not permit any neuroanatomical claims, since we do not have any neuroimaging data to relate to task performance, previous results showing additional aging effects in relational (spatial) binding conditions could have been driven by medial temporal lobe dysfunction that has been demonstrated in older people (Du et al., 2006; Raz et al., 2004). In agreement with this notion, we showed that neuropsychological tests that are assumed to rely on frontal functions explain a significant proportion of the variation in task performance. In contrast, test scores that are assumed to require functional integrity of the medial temporal lobe do not increase the explained variance. Importantly, this is only the case in middle-aged and older adults. In young adults, the pattern is opposite. Here, test scores that are assumed to rely on medial temporal lobe functions reliably explain a significant proportion of the variation in task performance, whereas frontal tests do not increase the amount of variation explained.

A possible explanation for this finding is that young and older adults adopt different strategies when performing the task (see e.g. Grady & Craik, 2000). The older adults may have relied mainly on low-resource working memory strategies. This is supported by the fact that in older adults, performance is best explained by 'frontal-based' neuropsychological tests. Even though the task at hand is primarily a 'prefrontal' working memory task, young adults may have improved their performance by using additional long-term memory strategies which were not available to older adults, arguably due to a hypo-functional hippocampus. This is supported by the finding that younger adults' performance is best explained by 'temporally-based' neuropsychological tests. However, these explanations remain speculative, as we did not systematically record strategy-usage.

With respect to the interference task, we found that it influenced performance, independent of aging. This is in contrast with a previous study showing that older adults are less efficient in filtering irrelevant information (Jost et al., 2011). Rather, it is in line with a study suggesting that inhibition is not a crucial mediator in the age-related decline in working memory (Borella, Carretti, & De Beni, 2008). The fact that an interfering task leads to worse performance confirms that binding processes require attention (D. Luck et al., 2010; W. D. Spencer & Raz, 1995; Wheeler & Treisman, 2002). Interestingly, relational binding is found to be more susceptible

to interference than conjunctive binding, which suggests that relational binding requires more attention than conjunctive binding. This supports the notion that conjunctive binding is a more automatic process (Ecker et al., 2013; Kubovy et al., 1999). It has been suggested that binding in a unitized or conjunctive fashion may involve familiarity, whereas relational binding relies primarily on recollection (Quamme, Yonelinas, & Normani, 2007).

The data revealed additional evidence in favour of the argument that relational binding requires more resources than conjunctive binding. That is, in the interfering condition, young adults´ relational binding performance drops to the level of older adults. In other words, young adults performing the relational binding condition with less attentional resources are similar to older adults' full-attention performance. This suggests that attention is a mediating factor in older adults' relational binding deficit. Interestingly, this effect is not observed in conjunctive binding, indicating that attention cannot be the sole mediating factor in this age-related conjunctive binding deficit. It has been argued before that the age-related decline in working memory is not associated to a deficit in binding, but rather to a decline in available resources (Bopp & Verhaeghen, 2009).

In contrast, the lack of an interaction effect between interference and group undermines this claim. This suggests that older adults are not more susceptible to an interfering task. Some studies argue that although both an interfering task and aging result in similar performance levels, the underlying mechanisms may differ (Castel & Craik, 2003; Naveh-Benjamin et al., 2004; Naveh-Benjamin, Guez, & Marom, 2003). For example, resource reduction may disrupt memory in general (i.e. memory for both item information and associative information), whereas aging may specifically disrupt associative mechanisms. From our study, we cannot conclude whether the similar performance of young adults with reduced resources and older adults is caused by the same underlying mechanisms. However, we clearly show that attentional resources are more important for relational binding than for conjunctive binding.

Together, these results indicate that working memory binding deficits are more likely driven by a general decline in reflective processes or attentional resources associated with frontal dysfunction, rather than by a decline in hippocampally mediated associative processes (see also W. D. Spencer & Raz, 1995). This is in line with literature stating that working memory binding tasks activate the frontal lobe (Poch et al., 2010; Prabhakaran, Narayanan, Zhao, & Gabrieli, 2000; Prince et al., 2005) and that aging affects the prefrontal cortex to a greater extent than the medial temporal lobe (Kalpouzos et al., 2009). In studies finding that specifically the medial temporal lobe is involved in binding tasks, the spatial component of the task may explain the findings.

Acknowledgements

We thank Karina Burger, Lieke van Lieshout, Iris Wensink and Marloes de Jonge for their assistance in collecting the data.

Chapter 9 Summary and Discussion

Memory problems are very common in people with brain disorders or diseases. Although memory has been researched quite extensively, some issues are still topic of discussion. In this thesis, I focused on the role of the medial temporal lobe in associative working memory and the interaction between working memory and episodic memory formation. In this chapter, I will summarize the main findings and relate these to the three hypotheses described and examined in this thesis. In short, these hypotheses provide the following possibilities regarding the role of the medial temporal lobe in working memory. First, the medial temporal lobe may be involved in working memory binding tasks because this brain structure is involved in relational memory in general. Second, medial temporal lobe activity during working memory tasks may reflect incidental long-term memory encoding processes. Third, medial temporal lobe activity is recruited when long-term memory processes are needed for additional support in processing information that exceeds working memory capacity. The studies described in this thesis aimed to examine these three hypotheses, using different paradigms and patient samples.

Summary of findings

Chapter two describes patients with early Alzheimer's disease, who performed a working memory binding task examining object-location memory (the Box Task) and a subsequent episodic memory task (the Object Relocation task). Working memory binding was found to be impaired in these patients and this deficit increased with growing set size, suggesting that working memory capacity was exceeded. Subsequent memory was impaired in the Alzheimer patients, but no episodic memory deficit was found for the smallest (3) and largest set size (8). The smallest set size is argued to be too easy for any effects to be found (ceiling effect). The largest set size may rely on residual long-term memory function during the working memory task, as working memory capacity may not suffice. These long-term memory processes may then result in a better long-term performance.

Chapter three describes a study in stroke patients. It was shown that these patients are impaired in working memory for single features (i.e., memory for objects and memory for locations), but performed at the level of controls in the conditions requiring working memory binding. In addition, patients showed no deficit in the subsequent episodic memory task. In short, patients with lesions that generally do not involve the medial temporal lobe show no deficits in working memory binding or subsequent episodic memory. Memory for single features may predominantly be subserved by the fronto-parietal working memory network, which is more susceptible to stroke.

In contrast to stroke patients, patients with unilateral anterior temporal lobectomy, described in **chapter four**, have selective medial temporal lobe damage. The working memory task applied here contrasted single-item memory with three types of binding. That is, conjunctive binding (object-color), spatial relational binding (object-location) and non-spatial relational binding (object-object). Patients were found to be impaired on the relational binding conditions (although only marginally on the spatial relational binding condition), but were not impaired on the conjunctive binding condition. Single-item memory was impaired for trials with long delays only. The relational memory hypothesis does not explain why deficits were found for single items. The notion of working memory overload fits the data better: both binding and longer delays result in an overload of working memory capacity. The medial temporal lobe is then recruited when working memory capacity does not suffice. The possibility of long-term encoding processes explaining medial temporal lobe involvement in working memory binding tasks cannot be excluded with this study.

In order to examine the notion that long-term encoding processes take place during working memory binding, I described a study in **chapter five** that was similar to the one in chapter four, but with an additional subsequent memory task. Patients with amnesia due to Korsakoff's syndrome performed a task in which house-face associations had to be maintained for either a short or a long delay. The patients showed a significant deficit in working memory performance, even at short delays. Since longer delays may induce long-term encoding processes, we hypothesized that controls would show better subsequent memory for item pairs processed during long delays as compared to item pairs processed during short delays. However, this is not what we observed, indicating that longer delays do not facilitate long-term encoding.

In an attempt to replicate and extend the results described in chapter five, we used the exact same paradigm in an aging study and a patient study (**chapter six**). The aging study confirmed our previous finding that longer delays do not improve subsequent memory, even in young adults who may have more working memory resources to complete the task. In the patient study, we assessed patients with Mild Cognitive Impairment and Alzheimer's dementia. With these patient groups, we replicated our previous findings in patients with Korsakoff's syndrome. These findings lead to the suggestion that working memory capacity is exceeded in this working memory binding task because of its associative component. Long-term memory processes are then used to support performance, which is why patients with amnesia fail on the task.

Chapter 7 examined whether the medial temporal lobe is involved in working memory binding tasks because of its general role in relational memory, or whether it is only involved when working memory capacity is exceeded. To this end, we

measured the precision with which participants could maintain the orientation of colored bars in working memory. Set size was manipulated in the task. Patients with Mild Cognitive Impairment or Alzheimer's dementia were impaired, although not this was not additionally affected by increasing set sizes. In addition, hippocampal volume was found to be related to performance, but specifically to performance in trials with smaller set sizes. I argue that not the number of items, but rather the serial position of the items is crucial. The findings suggest that subsequent items interfere with the contents of working memory.

In order to examine the effect of interference on working memory binding performance in different age groups, an interfering task was used in **chapter eight**. Conjunctive and relational binding were contrasted, as it had been suggested that relational binding is more sensitive to aging than conjunctive binding. Both types of binding were assessed using color-shape bindings, in order to be able to directly contrast them. The results show that relational binding is not affected more by increasing age than conjunctive binding. In contrast, relational binding is more sensitive to an interfering task than conjunctive binding. This may suggest that relational binding requires more resources. Since the performance of the older adults was not found to be more susceptible to the interfering task than the younger adults, attentional deficits cannot explain older adults' impaired performance.

Fitting the data with the hypotheses

Relational memory

This hypothesis states that the medial temporal lobe is involved in processing relational information in general, independent of whether it is to be remembered on the short or the long term (Cohen et al., 1999; Eichenbaum et al., 1994; Konkel & Cohen, 2009). The fact that both amnesic patients with Korsakoff's syndrome (chapter 5) and patients with Alzheimer's disease (chapters 2, 6 and 7) are impaired on working memory binding tasks is in line with this notion. In addition, the stroke patients (typically without medial temporal lobe involvement) described in chapter 3 did not show any binding problems. However, this evidence does not suffice in order to claim that it is only the relational aspect of the working memory tasks that result in medial temporal lobe involvement, as it does not exclude the other possible explanations. It may be too general as a valid explanation.

Incidental long-term encoding

If long-term encoding processes take place during working memory binding tasks, then longer delays could be argued to result in better subsequent episodic memory performance (Ezzyat & Olson, 2008; Nichols et al., 2006a). However, this is not in

line with the data presented in chapters 5 and 6. In both young and older healthy adults, no evidence was found that longer delays result in better subsequent memory. At least one other study found no difference in long-term memory performance as a function of delay length during the working memory task (Ranganath et al., 2005), although they did found hippocampal activation to correlate to successful subsequent memory performance. Only chapter 2 seems to provide some evidence in favor of this theory. In that study, larger set sizes may have promoted long-term encoding processes that improved subsequent episodic memory.

Working memory overload

Most evidence was found in favor of the notion that long-term memory processes support working memory performance when its capacity is exceeded (Jeneson et al., 2011, 2010; Jeneson & Squire, 2012). For example, the study described in chapter 2 showed that patients with Alzheimer's disease have larger deficits with increasing set size. Whereas healthy participants can benefit from supporting long-term memory processes, these patients cannot. However, note that we did not observe such an increasing deficit with increasing set size using the working memory precision task (chapter 7).

Both in chapters 4 and 6, it was suggested that the binding component in the tasks resulted in an overload of working memory capacity. The finding that maintaining single items also results in deficits in patients with selective medial temporal lobe damage argues against the relational memory theory. Only long-delay trials result in this deficit though, again supporting the notion that working memory capacity is exceeded when delays are long. When working memory capacity is exceeded, long-term memory processes may be recruited to support performance. Patients with medial temporal lobe dysfunction cannot optimally rely on this support, leading to a deficit on working memory tasks. Finally, the aging study in chapter 8 suggests that relational binding requires more working memory resources than conjunctive (or unitized) binding.

Integrating the three hypotheses

The three hypotheses that were examined, may not be strictly independent from each other. Overlap is specifically apparent for the long-term encoding hypothesis and the working memory overload hypothesis. When long-term memory processes are used to support performance in case of an overload of working memory capacity, incidental long-term encoding could take place. It could even be argued that there is considerable overlap between all three hypotheses. For example, using associative stimuli may enhance an overload of working memory capacity, which could induce incidental long-term encoding.

When taking into account all data presented in this thesis, it could be argued that most results are in line with the hypothesis of working memory overload. Although not all studies described in this thesis present results that are fully in line with this hypothesis, in general they support the notion that long-term processes are involved in working memory tasks especially when working memory capacity is exceeded. This can be driven either by adding an associative component or by extending delay periods. It is, however, not necessarily reflected in improved subsequent memory performance.

Difficulties in separating working memory and long-term memory processes

Practical difficulties

In this thesis I attempted to separate working memory processes from long-term memory processes by examining both within one behavioral paradigm. This proved to be complicated. Using two separate tests for the same studied material (i.e., short-term and long-term assessment) does not automatically separate the underlying processes. It remains a challenge to disentangle which processes influence performance at a behavioral level.

For example, it proved difficult to design a task in such a way that it would not elucidate floor or ceiling effects in either the patient or the control group. Using two similar tests for working memory and subsequent episodic memory brought an extra challenge to this effort. The working memory task could not be too easy, but the subsequent episodic memory task could not be too difficult. Care was taken to avoid ceiling and floor effects by extensive piloting, which proved successful in many participants of the studies presented here. However, we could not avoid that in some patients or older controls, floor effects were found.

Future studies could perhaps use simpler stimuli in order to avoid this problem, as it can be argued that houses and faces are complex stimuli. In addition, the complexity of the stimuli can induce long-term memory processes. However, several other studies using simple features, such as shape and color, found similar deficits in patients (Braun et al., 2011; Parra et al., 2011; Parra, Abrahams, Fabi, et al., 2009). Moreover, using basic features might lead to ceiling effects in the control group. Extensive piloting is probably the best way to find an optimal balance between floor effects in patients and ceiling effects in controls.

Theoretical difficulties

As apparent from this thesis, long-term memory processes are likely to support working memory performance when working memory capacity is exceeded. The

question is how and when exactly working memory capacity is exceeded. It can be argued that this is not necessarily related to a specific time interval, but rather to several other task requirements. As stated by Jeneson and Squire (2012):

"The key factors that determine whether working memory is sufficient to support performance, or whether performance must also depend on long-term memory, are the amount of information that can be held in mind and how amenable this information is to active rehearsal. If the capacity of working memory is exceeded, or if material cannot be effectively maintained by rehearsal (as can be the case for nonverbal material), performance must depend at least in part on long-term memory, even at short retention intervals." (p. 15-16).

In fact, many stimuli used in working memory tasks activate long-term memory or are held in mind using representations from long-term memory. Therefore, it could be questioned whether it is possible to strictly separate working memory from long-term memory merely based on the time interval. Others have argued that it would be more productive to design models of memory that do not assume distinctions based on the length of retention intervals (see e.g., Ranganath & Blumenfeld, 2005). Using processing modes to describe brain regions and their functions in memory would make more sense, as argued by Henke (2010). She states that the hippocampus rapidly encodes associations, independently of the delay length.

In sum, when task demands, representation types and processing modes are determining whether something is remembered on the short or the long term, there may be no need to define separate memory systems.

Strengths and limitations

A strong point of the research conducted as part of this thesis is that working memory and long-term memory were studied jointly, using similar stimuli and comparable task demands. Many studies addressing memory functions studied only working memory or only long-term memory, or used different tasks and stimuli for assessing working memory and long-term memory in the same sample (e.g., digit span versus word list learning). As argued before in this thesis, when interpreting working memory task performance, note that participants may have needed support from long-term memory processes. Thus, the interaction of working memory and long-term memory processes cannot be ignored when drawing conclusions about the specificity of performance differences in working memory tasks or its neural representations.

The majority of the studies described in the present thesis are patient studies. One point of critique that is often raised concerns the extent and localisation of

patients' lesions and the certainty with which conclusions about the function of specific brain regions can be drawn from patients' performance. Indeed, the brain damage in patients with Alzheimer's disease or Korsakoff's syndrome is not limited to, for example, the hippocampus, or even to the medial temporal lobe. Therefore, conclusions drawn from studies examining these patient populations should always be considered with some care, especially when no neuroimaging data is available to confirm the lesions of the participants. Although no neuroimaging data allowing for detailed volumetric analyses of the lesions were available in most of the studies in this thesis, the patients described were all diagnosed using available neuroimaging data, also excluding other etiologies.

There is one group of patients described in the present thesis that did have selective lesions: the patients with epilepsy who were surgically treated for their intractable seizures. These patients presented with selective lesions in the anterior temporal lobe. However, the lesions were all unilateral, not resulting in the classic 'amnesic syndrome' that was described in patients like H.M. (Scoville & Milner, 1957; Squire, 2009b). In addition, it could be argued that the prolonged existence of a condition like epilepsy may have altered the normal development of neural representation of cognitive functions in general.

Most ideally, patients with bilateral lesions, selective to the medial temporal lobe (or more specifically, the hippocampus) should be studied, when addressing memory functions. However, those selectively lesioned patients are very hard to find. See for example the studies by Squire and colleagues, which describe single cases (Zola-Morgan, Squire, & Amaral, 1986) or groups of only three to six patients with lesions limited to the hippocampus (Manns & Squire, 2001; Reed & Squire, 1997; Stark, Bayley, & Squire, 2002). This results in many practical issues, limited methodological strength and also preventing a large number of studies to be done. Therefore, in my view, studying different patient populations with one thing in common (i.e., medial temporal lobe dysfunction) provides with valuable insights into memory functions.

It can be questioned whether patient studies are still valuable in an era of neuroimaging techniques. Despite the abovementioned limitations, patient studies have some advantages in comparison to neuroimaging studies. Whereas neuroimaging data provide only correlational data, lesion studies provide knowledge on the necessity of brain regions in specific tasks. A combined approach, converging evidence from both imaging and lesion studies, might be most fruitful in the future. Concerning the topic of the current thesis, some neuroimaging studies have been performed using paradigms similar to the ones used here (Bergmann, Kiemeneij, Fernández, & Kessels, 2013; Bergmann et al., 2012). These studies suggest that activation observed in for example the hippocampus should be attributed to long-term memory processes that are involved in working memory tasks.

Clinical implications

The studies presented in this thesis do not only have implications for theoretical models of memory. Clinical implications can be drawn as well. In general clinical practice, when examining patients with mainly episodic memory problems, limited attention is given to working memory. In fact, standard neuropsychological tests (such as digit or spatial span tasks) most often do not reveal any difficulties on working memory tasks in patients with for example Alzheimer's disease. However, the data presented in this thesis shows that several patient groups with medial temporal lobe dysfunction have deficits in working memory. Previous studies by Belleville and colleagues have even suggested that working memory deficits in Mild Cognitive Impairment may predict conversion to Alzheimer's dementia (Belleville, Chertkow, & Gauthier, 2007b; Gagnon & Belleville, 2011).

In line with these findings, I argue that more effort should be undertaken to examine working memory problems in patients with medial temporal lobe dysfunction. More complex working memory tasks should be used in order to detect working memory deficits, as it is apparent from my studies that these deficits only arise when working memory capacity is exceeded. Neuropsychological tasks, developed based on n-back tasks or developed in order to assess episodic buffer functioning, would provide an opportunity to more specifically address working memory deficits in patients with medial temporal lobe dysfunction. Some effort has been undertaken to develop such tasks. For example, the CANTAB (J. Fray, W. Robbins, & J. Sahakian, 1996; Robbins et al., 1994, 1998; Sahakian & Owen, 1992) includes working memory subtests that are more complex and demanding than simple forward and backward span tasks. However, the (Dutch) norms for older participants may not be optimal. Another example is the Spatial Addition subtest from the Wechsler Memory Scale – fourth edition (David Wechsler, 2009), which is currently being translated and validated for use in the Netherlands. Furthermore, working memory binding tasks may become useful in differentiating between healthy and pathological aging, as stated in chapter 6.

Future directions

There are several issues that remain open to discussion and should be investigated further in future research. For example, if exceeding working memory capacity results in involvement of long-term memory processes, it remains to be specified which exact circumstances evoke this effect. I have suggested that associative processes, increasing working memory load and long delays lead working memory capacity to exceed. However, this should be further specified: there could be

specific types of binding that require support from long-term memory processes. As described in chapters 4 and 8, it could be that conjunctive bindings are able to be formed and maintained within the limits of working memory capacity, whereas relational bindings are not. Similar ideas have also been suggested by others (e.g. Ecker et al., 2013; Mayes et al., 2007; Piekema et al., 2010). In addition, certain stimuli may activate semantic representations in long-term memory evoking long-term memory involvement. These are issues that should be further examined.

Conclusion

The studies presented in this thesis examined the interaction between working memory and long-term memory processes. As these two are closely linked, every memory researcher should consider the impact of long-term memory processes on the working memory task used. That is, when patients with hippocampal lesions perform deficiently on a working memory task, this does not automatically mean that these patients have a problem with working memory processes, as it can also indicate that long-term memory processes are involved in the task. Likewise, neuroimaging studies showing hippocampal activation during a working memory task, may also reflect activation related to (incidental) long-term encoding processes.

In general, this thesis shows that more consideration should be given to the intimate relationship between working memory and long-term memory processes. The 'boxology' model by Squire (2004; 2009a) states that "memory is composed of multiple systems with different operating principles and different neuroanatomy" (Squire, 2009a, p. 12711). This sometimes results researchers to think that different memory systems are functioning independently and, as a result, can be studied in isolation. When studying memory, it should always be considered that multiple processes support performance. The present thesis is a first step in the process of disentangling which processes are involved in which specific memory tasks.

References
Nederlandse samenvatting
Dankwoord
Curriculum Vitae
Donders Series

References

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., ... Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*, *7*, 270–9. doi:10.1016/j.jalz.2011.03.008

Allen, R. J., Hitch, G. J., Mate, J., & Baddeley, A. D. (2012). Feature binding and attention in working memory: A resolution of previous contradictory findings. *The Quarterly Journal of Experimental Psychology*. doi:10.1080/17470218.2012.687384

American Psychiatric Association. (2000). *DSM-IV-TR*.

Atkinson, R. C., & Shiffrin, R. M. (1968). Human Memory: A Proposed System and its Control Processes. In Kenneth W. Spence and Janet Taylor Spence (Ed.), *Psychology of Learning and Motivation* (Vol. Volume 2, pp. 89–195). Academic Press. Retrieved from http://www.sciencedirect.com/science/article/pii/S0079742108604223

Baddeley, A. D. (1981). The concept of working memory: A view of its current state and probable future development. *Cognition*, *10*(1-3), 17–23. doi:10.1016/0010-0277(81)90020-2

Baddeley, A. D. (1996). Exploring the central executive. *The Quarterly Journal of Experimental Psychology: Section A*, *49*(1), 5–28.

Baddeley, A. D. (2000). The episodic buffer: a new component of working memory? *Trends Cogn Sci*, *4*, 417–423.

Baddeley, A. D. (2003). Working memory: looking back and looking forward. *Nat Rev Neurosci*, *4*, 829–39. doi:10.1038/nrn1201

Baddeley, A. D. (2007). *Working Memory, Thought and Action*. Oxford: Oxford University Press.

Baddeley, A. D. (2012). Working Memory: Theories, Models, and Controversies. *Annual Review of Psychology*, *63*, 1–29. doi:10.1146/annurev-psych-120710-100422

Baddeley, A. D., Allen, R. J., & Hitch, G. J. (2011). Binding in visual working memory: the role of the episodic buffer. *Neuropsychologia*, *49*, 1393–400. doi:10.1016/j.neuropsychologia.2010.12.042

Baddeley, A. D., Allen, R., & Vargha-Khadem, F. (2010). Is the hippocampus necessary for visual and verbal binding in working memory? *Neuropsychologia*, *48*, 1089–1095. doi:10.1016/j.neuropsychologia.2009.12.009

Baddeley, A. D., & Hitch, G. J. (1974). Working memory. *The Psychology of Learning and Motivation*, *8*, 47–89.

Baddeley, A. D., Jarrold, C., & Vargha-Khadem, F. (2011). Working Memory and the Hippocampus. *Journal of Cognitive Neuroscience*, *23*(12), 3855–3861. doi:10.1162/jocn_a_00066

Bastin, C., & Van der Linden, M. (2006). The effects of aging on the recognition of different types of associations. *Experimental Aging Research*, *32*, 61–77. doi:10.1080/03610730500326291

Bays, P. M., Catalao, R. F. G., & Husain, M. (2009). The precision of visual working memory is set by allocation of a shared resource. *Journal of Vision*, *9*. doi:10.1167/9.10.7

Bays, P. M., Wu, E. Y., & Husain, M. (2011). Storage and binding of object features in visual working memory. *Neuropsychologia*, *49*(6), 1622–1631.

Belleville, S., Chertkow, H., & Gauthier, S. (2007a). Working memory and control of attention in persons with Alzheimer's disease and mild cognitive impairment. *Neuropsychology*, *21*(4), 458–469. doi:10.1037/0894-4105.21.4.458

Belleville, S., Chertkow, H., & Gauthier, S. (2007b). Working memory and control of attention in persons with Alzheimer's disease and mild cognitive impairment. *Neuropsychology*, *21*(4), 458–469. doi:10.1037/0894-4105.21.4.458

Belleville, S., Peretz, I., & Malenfant, D. (1996). Examination of the working memory components in normal aging and in dementia of the Alzheimer type. *Neuropsychologia*, *34*(3), 195–207. doi:10.1016/0028-3932(95)00097-6

Bergmann, H. C., Kiemeneij, A., Fernández, G., & Kessels, R. P. C. (2013). Early and late stages of working-memory maintenance contribute differentially to long-term memory formation. *Acta Psychologica*, *143*(2), 181–190. doi:10.1016/j.actpsy.2013.02.009

Bergmann, H. C., Rijpkema, M., Fernández, G., & Kessels, R. P. C. (2012). Distinct neural correlates of associative working memory and long-term memory encoding in the medial temporal lobe. *Neuroimage*, *63*, 989–97. doi:10.1016/j.neuroimage.2012.03.047

Berlingeri, M., Bottini, G., Basilico, S., Silani, G., Zanardi, G., Sberna, M., ... Paulesu, E. (2008). Anatomy of the episodic buffer: A voxel-based morphometry study in patients with dementia. *Behavioural Neurology*, *19*, 29–34.

Blumenfeld, R. S., Parks, C. M., Yonelinas, A. P., & Ranganath, C. (2011). Putting the pieces together: the role of dorsolateral prefrontal cortex in relational memory encoding. *Journal of Cognitive Neuroscience*, *23*(1), 257–265.

Blumenfeld, R. S., & Ranganath, C. (2006). Dorsolateral Prefrontal Cortex Promotes Long-Term Memory Formation through Its Role in Working Memory Organization. *Journal of Neuroscience*, *26*(3), 916–925. doi:10.1523/JNEUROSCI.2353-05.2006

Blumenfeld, R. S., & Ranganath, C. (2007). Prefrontal Cortex and Long-Term Memory Encoding: An Integrative Review of Findings from Neuropsychology and Neuroimaging. *The Neuroscientist*, *13*(3), 280–291. doi:10.1177/1073858407299290

Bopp, K. L., & Verhaeghen, P. (2009). Working memory and aging: Separating the effects of content and context. *Psychology and Aging*, *24*(4), 968–980. doi:10.1037/a0017731

Borella, E., Carretti, B., & De Beni, R. (2008). Working memory and inhibition across the adult life-span. *Acta Psychologica*, *128*(1), 33–44. doi:10.1016/j.actpsy.2007.09.008

Braun, M., Finke, C., Ostendorf, F., Lehmann, T. N., Hoffmann, K. T., & Ploner, C. J. (2008). Reorganization of associative memory in humans with long-standing hippocampal damage. *Brain*, *131*, 2742–2750. doi:10.1093/Brain/Awn191

Braun, M., Weinrich, C., Finke, C., Ostendorf, F., Lehmann, T. N., & Ploner, C. J. (2011). Lesions affecting the right hippocampal formation differentially impair short-term memory of spatial and nonspatial associations. *Hippocampus*, *21*, 309–18. doi:10.1002/hipo.20752

Brickman, A. M., Zimmerman, M. E., Paul, R. H., Grieve, S. M., Tate, D. F., Cohen, R. A., ... Gordon, E. (2006). Regional white matter and neuropsychological functioning across the adult lifespan. *Biol Psychiatry*, *60*, 444–53. doi:10.1016/j.biopsych.2006.01.011

Brockmole, J. R., & Logie, R. H. (2013). Age-Related Change in Visual Working Memory: A Study of 55,753 Participants Aged 8–75. *Frontiers in Psychology*, *4*. doi:10.3389/fpsyg.2013.00012

Brockmole, J. R., Parra, M. A., Della Sala, S., & Logie, R. H. (2008). Do binding deficits account for age-related decline in visual working memory? *Psychon Bull Rev*, *15*, 543–7.

Brokate, B., Hildebrandt, H., Eling, P., Fichtner, H., Runge, K., & Timm, C. (2003). Frontal lobe dysfunctions in Korsakoff's syndrome and chronic alcoholism: Continuity or discontinuity? *Neuropsychology*, *17*(3), 420–428. doi:10.1037/0894-4105.17.3.420

Brown, L. A., & Brockmole, J. R. (2010). The role of attention in binding visual features in working memory: evidence from cognitive ageing. *Q J Exp Psychol (Hove)*, *63*, 2067–79. doi:10.1080/17470211003721675

Buffalo, E. A., Reber, P. J., & Squire, L. R. (1998). The human perirhinal cortex and recognition memory. *Hippocampus*, *8*, 330–9. doi:10.1002/(SICI)1098-1063(1998)8:4<330::AID-HIPO3>3.0.CO;2-L

Cabeza, R., Ciaramelli, E., Olson, I. R., & Moscovitch, M. (2008). The parietal cortex and episodic memory: an attentional account. *Nature Reviews Neuroscience*, *9*(8), 613–625. doi:10.1038/nrn2459

Castel, A. D., & Craik, F. I. M. (2003). The Effects of Aging and Divided Attention on Memory for Item and Associative Information. *Psychology and Aging*, *18*(4), 873–885. doi:10.1037/0882-7974.18.4.873

Chalfonte, B. L., & Johnson, M. K. (1996). Feature memory and binding in young and older adults. *Mem Cognit*, *24*, 403–16.

Cohen, N. J., Poldrack, R. A., & Eichenbaum, H. (1997). Memory for items and memory for relations in the procedural/declarative memory framework. *Memory*, *5*, 131–78. doi:10.1080/741941149

Cohen, N. J., Ryan, J., Hunt, C., Romine, L., Wszalek, T., & Nash, C. (1999). Hippocampal system and declarative (relational) memory: summarizing the data from functional neuroimaging studies. *Hippocampus*, *9*(1), 83–98.

Cowan, N. (1999). An Embedded-Processes Model of working memory. In A. Miyake & P. Shah (Eds.), *Models of working memory: Mechanisms of active maintenance and executive control* (pp. 62–101). New York, NY, US: Cambridge University Press.

Cowan, N. (2008). What are the differences between long-term, short-term, and working memory? *Progress in Brain Research*, *169*, 323–338. doi:10.1016/S0079-6123(07)00020-9

Cowey, C. M. (1996). The Hippocampus: A "; Working Memory" Structure? The Effect of Hippocampal Sclerosis on Working Memory. *Memory*, *4*(1), 19–30.

Craik, F. I., & McDowd, J. M. (1987). Age differences in recall and recognition. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *13*(3), 474–479. doi:10.1037/0278-7393.13.3.474

Crane, J., & Milner, B. (2005). What went where? Impaired object-location learning in patients with right hippocampal lesions. *Hippocampus*, *15*, 216–31. doi:10.1002/hipo.20043

Curtis, C. E. (2006). Prefrontal and parietal contributions to spatial working memory. *Neuroscience*, *139*, 173–180. doi:10.1016/j.neuroscience.2005.04.070

Curtis, C. E., & D'Esposito, M. (2003). Persistent activity in the prefrontal cortex during working memory. *Trends in Cognitive Sciences*, *7*(9), 415–423.

D'Esposito, M. (2007). From cognitive to neural models of working memory. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *362*(1481), 761–772. doi:10.1098/rstb.2007.2086

Davachi, L., & Wagner, A. D. (2002). Hippocampal contributions to episodic encoding: insights from relational and item-based learning. *J Neurophysiol*, *88*, 982–90.

Davidson, P. S. R., Anaki, D., Ciaramelli, E., Cohn, M., Kim, A. S. N., Murphy, K. J., ... Levine, B. (2008). Does lateral parietal cortex support episodic memory? *Neuropsychologia*, *46*(7), 1743–1755. doi:10.1016/j.neuropsychologia.2008.01.011

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (1987). *The California Verbal Learning Test: Adult version manual*. San Antonio: Psychological Corporation.

Della Sala, S., Parra, M. A., Fabi, K., Luzzi, S., & Abrahams, S. (2012). Short-term memory binding is impaired in AD but not in non-AD dementias. *Neuropsychologia*, *50*, 833–40. doi:10.1016/j.neuropsychologia.2012.01.018

Du, A. T., Schuff, N., Chao, L. L., Kornak, J., Jagust, W. J., Kramer, J. H., ... Weiner, M. W. (2006). Age effects on atrophy rates of entorhinal cortex and hippocampus. *Neurobiol Aging*, *27*, 733–40. doi:10.1016/j.neurobiolaging.2005.03.021

Ecker, U. K. H., Maybery, M., & Zimmer, H. D. (2013). Binding of intrinsic and extrinsic features in working memory. *Journal of Experimental Psychology: General*, *142*(1), 218–234. doi:10.1037/a0028732

Eichenbaum, H., Otto, T., & Cohen, N. J. (1994). Two functional components of the hippocampal memory system. *Behavioral and Brain Sciences*, *17*(03), 449–472.

Eichenbaum, H., Yonelinas, A. P., & Ranganath, C. (2007). The medial temporal lobe and recognition memory. *Annual Review of Neuroscience*, *30*, 123–152. doi:10.1146/annurev.neuro.30.051606.094328

Elsley, J. V., & Parmentier, F. B. R. (2009). Is verbal-spatial binding in working memory impaired by a concurrent memory load? *Quarterly Journal of Experimental Psychology*, *62*, 1696–1705. doi:10.1080/17470210902811231

Ezzyat, Y., & Olson, I. R. (2008). The medial temporal lobe and visual working memory: comparisons across tasks, delays, and visual similarity. *Cognitive, Affective, & Behavioral Neuroscience*, *8*(1), 32–40.

Funahashi, S., Bruce, C. J., & Goldman-Rakic, P. S. (1989). Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. *Journal of Neurophysiology*, *61*(2), 331–349.

Fuster, J. M., & Alexander, G. E. (1971). Neuron Activity Related to Short-Term Memory. *Science*, *173*(3997), 652–654. doi:10.1126/science.173.3997.652

Gagnon, L. G., & Belleville, S. (2011). Working memory in mild cognitive impairment and Alzheimer's disease: Contribution of forgetting and predictive value of complex span tasks. *Neuropsychology*, *25*(2), 226–236. doi:10.1037/a0020919

Gazzaniga, M. S., Ivry, R. B., & Mangun, G. R. (2002). *Cognitive Neuroscience: The Biology of the Mind* (2nd ed.). New York: Norton & Company.

Gooding, P. A., Isaac, C. L., & Mayes, A. R. (2005). Prose recall and amnesia: more implications for the episodic buffer. *Neuropsychologia*, *43*(4), 583–587. doi:10.1016/j.neuropsychologia.2004.07.004

Gorgoraptis, N., Catalao, R. F., Bays, P. M., & Husain, M. (2011). Dynamic updating of working memory resources for visual objects. *J Neurosci*, *31*, 8502–11. doi:10.1523/JNEUROSCI.0208-11.2011

Grady, C. L., & Craik, F. I. (2000). Changes in memory processing with age. *Current Opinion in Neurobiology*, *10*(2), 224–231.

Guarch, J., Marcos, T., Salamero, M., Gasto, C., & Blesa, R. (2008). Mild cognitive impairment: a risk indicator of later dementia, or a preclinical phase of the disease? *Int J Geriatr Psychiatry*, *23*, 257–65. doi:10.1002/gps.1871

Hanaki, R., Abe, N., Fujii, T., Ueno, A., Nishio, Y., Hiraoka, K., ... Mori, E. (2011). The effects of aging and Alzheimer's disease on associative recognition memory. *Neurological Sciences*, *32*, 1115–1122. doi:10.1007/s10072-011-0748-4

Hannula, D. E., & Ranganath, C. (2008). Medial temporal lobe activity predicts successful relational memory binding. *J Neurosci*, *28*, 116–24. doi:10.1523/JNEUROSCI.3086-07.2008

Hannula, D. E., Tranel, D., & Cohen, N. J. (2006). The long and the short of it: relational memory impairments in amnesia, even at short lags. *J Neurosci*, *26*, 8352–9. doi:10.1523/JNEUROSCI.5222-05.2006

Henke, K. (2010). A model for memory systems based on processing modes rather than consciousness. *Nature Reviews Neuroscience*, *11*(7), 523–532.

Henke, K., Buck, A., Weber, B., & Wieser, H. G. (1997). Human hippocampus establishes associations in memory. *Hippocampus*, *7*(3), 249–256.

Henke, K., Weber, B., Kneifel, S., Wieser, H. G., & Buck, A. (1999). Human hippocampus associates information in memory. *Proceedings of the National Academy of Sciences*, *96*(10), 5884–5889.

J. Fray, P., W. Robbins, T., & J. Sahakian, B. (1996). Neuorpsychiatyric applications of CANTAB. *International Journal of Geriatric Psychiatry*, *11*(4), 329–336. doi:10.1002/(SICI)1099-1166(199604)11:4<329::AID-GPS453>3.0.CO;2-6

Jaillard, A., Naegele, B., Trabucco-Miguel, S., LeBas, J. F., & Hommel, M. (2009). Hidden dysfunctioning in subacute stroke. *Stroke*, *40*, 2473–9. doi:10.1161/STROKEAHA.108.541144

James, W. (1890). *The Principles of Psychology*. New York: Henry Holt.

Jeneson, A., Mauldin, K. N., Hopkins, R. O., & Squire, L. R. (2011). The role of the hippocampus in retaining relational information across short delays: The importance of memory load. *Learning & Memory*, *18*, 301–305. doi:10.1101/Lm.2010711

Jeneson, A., Mauldin, K. N., & Squire, L. R. (2010). Intact Working Memory for Relational Information after Medial Temporal Lobe Damage. *Journal of Neuroscience*, *30*, 13624–13629. doi:10.1523/Jneurosci.2895-10.2010

Jeneson, A., & Squire, L. R. (2012). Working memory, long-term memory, and medial temporal lobe function. *Learning & Memory*, *19*, 15–25. doi:10.1101/lm.024018.111

Jeneson, A., Wixted, J. T., Hopkins, R. O., & Squire, L. R. (2012). Visual Working Memory Capacity and the Medial Temporal Lobe. *Journal of Neuroscience*, *32*, 3584–3589. doi:10.1523/Jneurosci.6444-11.2012

Jonides, J., Lewis, R. L., Nee, D. E., Lustig, C. A., Berman, M. G., & Moore, K. S. (2008). The Mind and Brain of Short-Term Memory. *Annual Review of Psychology*, *59*(1), 193–224. doi:10.1146/annurev.psych.59.103006.093615

Jost, K., Bryck, R. L., Vogel, E. K., & Mayr, U. (2011). Are Old Adults Just Like Low Working Memory Young Adults? Filtering Efficiency and Age Differences in Visual Working Memory. *Cerebral Cortex*, *21*, 1147–1154. doi:10.1093/cercor/bhq185

Juengling, F. D., & Kassubek, J. (2003). Standardized calculation of brain parenchymal fraction: an approach to objective assessment of cerebral atrophy. *American Journal of Neuroradiology*, *24*(7), 1492–1493.

Kalpouzos, G., Chételat, G., Baron, J.-C., Landeau, B., Mevel, K., Godeau, C., Eustache, F. (2009). Voxel-based mapping of brain gray matter volume and glucose metabolism profiles in normal aging. *Neurobiology of Aging*, *30*(1), 112–124.

Kersten, A. W., & Earles, J. L. (2010). Effects of aging, distraction, and response pressure on the binding of actors and actions. *Psychology and Aging; Psychology and Aging*, *25*(3), 620.

Kessels, R. P. C., & Kopelman, M. D. (2012). Context Memory in Korsakoff's Syndrome. *Neuropsychology Review*, *22*(2), 117–131. doi:10.1007/s11065-012-9202-5

Kessels, R. P. C., Meulenbroek, O., Fernández, G., & Olde Rikkert, M. G. (2010). Spatial working memory in aging and mild cognitive impairment: effects of task load and contextual cueing. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*, *17*, 556–74. doi:10.1080/13825585.2010.481354

Kessels, R. P. C., Nys, G. M. S., Brands, A. M. A., Van den Berg, E., & Van Zandvoort, M. J. E. (2006). The modified Location Learning Test: Norms for the assessment of spatial memory function in neuropsychological patients. *Archives of Clinical Neuropsychology*, *21*, 841–846. doi:10.1016/j.acn.2006.06.015

Kessels, R. P. C., Postma, A., & de Haan, E. H. F. (1999). Object Relocation: a program for setting up, running, and analyzing experiments on memory for object locations. *Behav Res Methods Instrum Comput*, *31*, 423–8.

Kessels, R. P. C., Postma, A., Wester, A. J., & de Haan, E. H. F. (2000). Memory for object locations in Korsakoff's amnesia. *Cortex*, *36*, 47–57.

Kessels, R. P. C., van Zandvoort, M. J. E., Postma, A., Kappelle, L. J., & de Haan, E. H. F. (2000). The Corsi Block-Tapping Task: Standardization and Normative Data. *Applied Neuropsychology*, *7*(4), 252–258. doi:10.1207/S15324826AN0704_8

Kim, H. (2011). Neural activity that predicts subsequent memory and forgetting: a meta-analysis of 74 fMRI studies. *Neuroimage*, *54*(3), 2446–2461.

Konkel, A., & Cohen, N. J. (2009). Relational memory and the hippocampus: representations and methods. *Frontiers in Neuroscience*, *3*, 166–74. doi:10.3389/neuro.01.023.2009

Konkel, A., Warren, D. E., Duff, M. C., Tranel, D. N., & Cohen, N. J. (2008). Hippocampal amnesia impairs all manner of relational memory. *Frontiers in Human Neuroscience*, *2*. doi:10.3389/Neuro.09.015.2008

Kopelman, M. D. (2002). Disorders of memory. *Brain*, *125*(10), 2152–2190.

Kramer, J. H., Nelson, A., Johnson, J. K., Yaffe, K., Glenn, S., Rosen, H. J., & Miller, B. L. (2006). Multiple cognitive deficits in amnestic mild cognitive impairment. *Dement Geriatr Cogn Disord*, *22*, 306–11. doi:10.1159/000095303

Kubota, K., & Niki, H. (1971). Prefrontal cortical unit activity and delayed alternation performance in monkeys. *Journal of Neurophysiology*. Retrieved from http://psycnet.apa.org/?fa=main.doiLanding&uid=1972-00346-001

Kubovy, M., Cohen, D. J., & Hollier, J. (1999). Feature integration that routinely occurs without focal attention. *Psychonomic Bulletin & Review*, *6*, 183–203.

Lezak, M. D. (2004). *Neurpsychological assessment* (Fourth Edition.). New York: Oxford University Press.

Linden, D. E. J. (2007). The Working Memory Networks of the Human Brain. *The Neuroscientist*, *13*(3), 257–267. doi:10.1177/1073858406298480

Luck, D., Danion, J. M., Marrer, C., Pham, B. T., Gounot, D., & Foucher, J. (2010). The right parahippocampal gyrus contributes to the formation and maintenance of bound information in working memory. *Brain and Cognition*, *72*, 255–63. doi:10.1016/j.bandc.2009.09.009

Luck, S. J., & Vogel, E. K. (1997). The capacity of visual working memory for features and conjunctions. *Nature*, *390*, 279–281. doi:10.1038/36846

Maguire, E. A. (2001). Neuroimaging studies of autobiographical event memory. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, *356*(1413), 1441–1451.

Manns, J. R., & Squire, L. R. (2001). Perceptual learning, awareness, and the hippocampus. *Hippocampus*, *11*(6), 776–782. doi:10.1002/hipo.1093

Marshall, L., & Bays, P. M. (2013). Obligatory encoding of task-irrelevant features depletes working memory resources. *Journal of Vision*, *13*(2), 21–21. doi:10.1167/13.2.21

Mayes, A. R., MacDonald, C., Donlan, L., Pears, J., & Meudell, P. R. (1992). Amnesics have a disproportionately severe memory deficit for interactive context. *The Quarterly Journal of Experimental Psychology*, *45*, 265–97.

Mayes, A. R., Montaldi, D., & Migo, E. (2007). Associative memory and the medial temporal lobes. *Trends Cogn Sci*, *11*, 126–35. doi:10.1016/j.tics.2006.12.003

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Kawas, C. H., ... Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*, *7*, 263–9. doi:10.1016/j.jalz.2011.03.005

Meeter, M., & Murre, J. M. J. (2004). Consolidation of Long-Term Memory: Evidence and Alternatives. *Psychological Bulletin*, *130*(6), 843–857. doi:10.1037/0033-2909.130.6.843

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*, *24*(1), 167–202.

Milner, B., Johnsrude, I., & Crane, J. (1997). Right medial temporal-lobe contribution to object-location memory. *Philosophical Transactions of the Royal Society of London*, *352*, 1469–1474.

Mitchell, K. J., Johnson, M. K., Raye, C. L., & D'Esposito, M. (2000). fMRI evidence of age-related hippocampal dysfunction in feature binding in working memory. *Cognitive Brain Research*, *10*, 197–206.

Mitchell, K. J., Johnson, M. K., Raye, C. L., Mather, M., & D'Esposito, M. (2000). Aging and reflective processes of working memory: binding and test load deficits. *Psychology and Aging*, *15*, 527–41.

Mitchell, K. J., Raye, C. L., Johnson, M. K., & Greene, E. J. (2006). An fMRI investigation of short-term source memory in young and older adults. *Neuroimage*, *30*, 627–633. doi:10.1016/j.neuroimage.2005.09.039

Morris, J. C. (1993). The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. Retrieved from http://psycnet.apa.org/psycinfo/1994-19989-001

Moses, S. N., & Ryan, J. D. (2006). A comparison and evaluation of the predictions of relational and conjunctive accounts of hippocampal function. *Hippocampus*, *16*(1), 43–65. doi:10.1002/hipo.20131

Nadel, L., Samsonovich, A., Ryan, L., & Moscovitch, M. (2000). Multiple trace theory of human memory: Computational, neuroimaging, and neuropsychological results. *Hippocampus*, *10*(4), 352–368. doi:10.1002/1098-1063(2000)10:4<352::AID-HIPO2>3.0.CO;2-D

Naveh-Benjamin, M. (2000). Adult age differences in memory performance: Tests of an associative deficit hypothesis. *Journal of Experimental Psychology-Learning Memory and Cognition*, *26*, 1170–1187. doi:10.1037//0278-7393.26.2.1170

Naveh-Benjamin, M., Guez, J., Kilb, A., & Reedy, S. (2004). The associative memory deficit of older adults: Further support using face-name associations. *Psychology and Aging*, *19*, 541–546. doi:10.1037/0882-7974.19.3.541

Naveh-Benjamin, M., Guez, J., & Marom, M. (2003). The effects of divided attention at encoding on item and associative memory. *Memory & Cognition*, *31*, 1021–1035.

Naveh-Benjamin, M., Hussain, Z., Guez, J., & Bar-On, M. (2003). Adult age differences in episodic memory: Further support for an associative-deficit hypothesis. *Journal of Experimental Psychology-Learning Memory and Cognition*, *29*, 826–837. doi:10.1037/0278-7393.29.5.826

Nelson, H. E. (1982). *National Adult Reading Test (NART): For the Assessment of Premorbid Intelligence in Patients with Dementia: Test Manual*. NFER-Nelson.

Nichols, E. A., Kao, Y. C., Verfaellie, M., & Gabrieli, J. D. (2006a). Working memory and long-term memory for faces: Evidence from fMRI and global amnesia for involvement of the medial temporal lobes. *Hippocampus*, *16*, 604–16. doi:10.1002/hipo.20190

Nichols, E. A., Kao, Y. C., Verfaellie, M., & Gabrieli, J. D. (2006b). Working memory and long-term memory for faces: Evidence from fMRI and global amnesia for involvement of the medial temporal lobes. *Hippocampus*, *16*, 604–16. doi:10.1002/hipo.20190

Old, S. R., & Naveh-Benjamin, M. (2008). Differential effects of age on item and associative measures of memory: A meta-analysis. *Psychology and Aging*, *23*, 104–118. doi:10.1037/0882-7974.23.1.104

Olson, I. R., Page, K., Moore, K. S., Chatterjee, A., & Verfaellie, M. (2006). Working memory for conjunctions relies on the medial temporal lobe. *The Journal of Neuroscience*, *26*, 4596–601. doi:10.1523/JNEUROSCI.1923-05.2006

Oslin, D., Atkinson, R. M., Smith, D. M., & Hendrie, H. (1998). Alcohol related dementia: proposed clinical criteria. *International Journal of Geriatric Psychiatry*, *13*(4), 203–212.

Owen, A. M., Downes, J. J., Sahakian, B. J., Polkey, C. E., & Robbins, T. W. (1990). Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia*, *28*, 1021–34.

Parkin, A. J. (1998). The central executive does not exist. *Journal of the International Neuropsychological Society*, *4*(5), 518–522.

Parra, M. A., Abrahams, S., Fabi, K., Logie, R., Luzzi, S., & Della Sala, S. (2009). Short-term memory binding deficits in Alzheimer's disease. *Brain*, *132*, 1057–66. doi:10.1093/brain/awp036

Parra, M. A., Abrahams, S., Logie, R. H., & Della Sala, S. (2009). Age and binding within-dimension features in visual short-term memory. *Neurosci Lett*, *449*, 1–5. doi:10.1016/j.neulet.2008.10.069

Parra, M. A., Abrahams, S., Logie, R. H., & Della Sala, S. (2010). Visual short-term memory binding in Alzheimer's disease and depression. *Journal of Neurology*, *257*(7), 1160–1169. doi:10.1007/s00415-010-5484-9

Parra, M. A., Fabi, K., Luzzi, S., Cubelli, R., Hernandez Valdez, M., & Della Sala, S. (2013). Relational and conjunctive binding functions dissociate in short-term memory. *Neurocase*, 1–11. doi:10.1080/13554794.2013.860177

Parra, M. A., Sala, S. D., Abrahams, S., Logie, R. H., Mendez, L. G., & Lopera, F. (2011). Specific deficit of colour-colour short-term memory binding in sporadic and familial Alzheimer's disease. *Neuropsychologia*, *49*, 1943–52. doi:10.1016/j.neuropsychologia.2011.03.022

Patenaude, B. (2007). *Bayesian Statistical Models of Shape and Appearance for Subcortical Brain Segmentation.* University of Oxford.

Pertzov, Y., Miller, T. D., Gorgoraptis, N., Caine, D., Schott, J. M., Butler, C., & Husain, M. (2013). Binding deficits in memory following medial temporal lobe damage in patients with voltage-gated potassium channel complex antibody-associated limbic encephalitis. *Brain*. doi:10.1093/brain/awt129

Petersen, R. C., Doody, R., Kurz, A., Mohs, R. C., Morris, J. C., Rabins, P. V., ... Winblad, B. (2001). Current concepts in mild cognitive impairment. *Archives of Neurology*, *58*(12), 1985.

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: clinical characterization and outcome. *Archives of Neurology*, *56*(3), 303.

Piekema, C., Fernández, G., Postma, A., Hendriks, M. P., Wester, A. J., & Kessels, R. P. C. (2007). Spatial and non-spatial contextual working memory in patients with diencephalic or hippocampal dysfunction. *Brain Res*, *1172*, 103–9. doi:10.1016/j.brainres.2007.07.066

Piekema, C., Kessels, R. P. C., Mars, R. B., Petersson, K. M., & Fernández, G. (2006). The right hippocampus participates in short-term memory maintenance of object-location associations. *Neuroimage*, *33*, 374–82. doi:10.1016/j.neuroimage.2006.06.035

Piekema, C., Kessels, R. P. C., Rijpkema, M., & Fernández, G. (2009). The hippocampus supports encoding of between-domain associations within working memory. *Learning & Memory*, *16*, 231–4. doi:10.1101/lm.1283109

Piekema, C., Rijpkema, M., Fernández, G., & Kessels, R. P. C. (2010). Dissociating the neural correlates of intra-item and inter-item working-memory binding. *PLoS One*, *5*, e10214. doi:10.1371/journal.pone.0010214

Poch, C., Campo, P., Parmentier, F. B. R., Ruiz-Vargas, J. M., Elsley, J. V., Castellanos, N. P., ... del Pozo, F. (2010). Explicit processing of verbal and spatial features during letter-location binding modulates oscillatory activity of a fronto-parietal network. *Neuropsychologia*, *48*, 3846–3854. doi:10.1016/j.neuropsychologia.2010.09.015

Prabhakaran, V., Narayanan, K., Zhao, Z., & Gabrieli, J. D. E. (2000). Integration of diverse information in working memory within the frontal lobe. *Nature Neuroscience*, *3*, 85–90.

Prince, S. E., Daselaar, S. M., & Cabeza, R. (2005). Neural correlates of relational memory: Successful encoding and retrieval of semantic and perceptual associations. *Journal of Neuroscience*, *25*, 1203–1210. doi:10.1523/Jneurosci.2540-04.2005

Qin, S., Rijpkema, M., Tendolkar, I., Piekema, C., Hermans, E. J., Binder, M., Fernández, G. (2009). Dissecting medial temporal lobe contributions to item and associative memory formation. *NeuroImage*, *46*(3), 874–881. doi:10.1016/j.neuroimage.2009.02.039

Quamme, J. R., Yonelinas, A. P., & Normani, K. A. (2007). Effect of unitization on associative recognition in amnesia. *Hippocampus*, *17*, 192–200. doi:10.1002/Hipo.20257

Ranganath, C., & Blumenfeld, R. S. (2005). Doubts about double dissociations between short- and long-term memory. *Trends in Cognitive Sciences*, *9*, 374–80. doi:10.1016/j.tics.2005.06.009

Ranganath, C., Cohen, M. X., & Brozinsky, C. J. (2005). Working memory maintenance contributes to long-term memory formation: neural and behavioral evidence. *Journal of Cognitive Neuroscience*, *17*(7), 994–1010.

Raz, N., Rodrigue, K. M., Head, D., Kennedy, K. M., & Acker, J. D. (2004). Differential aging of the medial temporal lobe: a study of a five-year change. *Neurology*, *62*, 433–8.

Reed, J. M., & Squire, L. R. (1997). Impaired recognition memory in patients with lesions limited to the hippocampal formation. *Behavioral Neuroscience*, *111*(4), 667–675. doi:10.1037/0735-7044.111.4.667

Reitan, R. M. (1985). *The Halstead-Reitan Neuropsychological Test Battery: theory and clinical interpretation*. Tucson: Neuropsychology Press.

Repovs, G., & Baddeley, A. (2006). The multi-component model of working memory: Explorations in experimental cognitive psychology. *Neuroscience*, *139*, 5–21. doi:10.1016/j.neuroscience.2005.12.061

Robbins, T. W., James, M., Owen, A. M., Sahakian, B. J., Lawrence, A. D., McInnes, L., & Rabbitt, P. M. (1998). A study of performance on tests from the CANTAB battery sensitive to frontal lobe dysfunction in a large sample of normal volunteers: implications for theories of executive functioning and cognitive aging. Cambridge Neuropsychological Test Automated Battery. *Journal of the International Neuropsychological Society: JINS*, *4*(5), 474–490.

Robbins, T. W., James, M., Owen, A. M., Sahakian, B. J., McInnes, L., & Rabbitt, P. (1994). Cambridge Neuropsychological Test Automated Battery (CANTAB): A Factor Analytic Study of a Large Sample of Normal Elderly Volunteers. *Dementia and Geriatric Cognitive Disorders*, *5*(5), 266–281. doi:10.1159/000106735

Rossi-Arnaud, C., Pieroni, L., & Baddeley, A. (2006). Symmetry and binding in visuo-spatial working memory. *Neuroscience*, *139*, 393–400. doi:10.1016/j.neuroscience.2005.10.048

Rottschy, C., Langner, R., Dogan, I., Reetz, K., Laird, A. R., Schulz, J. B., ... Eickhoff, S. B. (2012). Modelling neural correlates of working memory: a coordinate-based meta-analysis. *Neuroimage*, *60*, 830–46. doi:10.1016/j.neuroimage.2011.11.050

Ruchkin, D. S., Grafman, J., Cameron, K., & Berndt, R. S. (2003). Working memory retention systems: A state of activated long-term memory. *Behavioral and Brain Sciences*, *26*, 709–+.

Sahakian, B. J., & Owen, A. M. (1992). Computerized assessment in neuropsychiatry using CANTAB: discussion paper. *Journal of the Royal Society of Medicine*, *85*(7), 399–402.

Salthouse, T. A. (1990). Working Memory as a Processing Resource in Cognitive Aging. *Developmental Review*, *10*, 101–124.

Salthouse, T. A. (2010). Selective review of cognitive aging. *Journal of the International Neuropsychological Society*, *16*(05), 754–760. doi:10.1017/S1355617710000706

Sander, M. C., Lindenberger, U., & Werkle-Bergner, M. (2012). Lifespan age differences in working memory: A two-component framework. *Neuroscience & Biobehavioral Reviews*, *36*(9), 2007–2033. doi:10.1016/j.neubiorev.2012.06.004

Schmand, B. A., Bakker, D., Saan, R. J., & Louman, J. (1991). De Nederlandse Leestest voor Volwassenen: een maat voor het premorbide intelligentieniveau. [The Dutch Adult Reading Test: A measure of premorbid intelligence.]. *Tijdschrift Voor Gerontologie En Geriatrie*, *22*, 15–19.

Schon, K., Hasselmo, M. E., Lopresti, M. L., Tricarico, M. D., & Stern, C. E. (2004). Persistence of parahippocampal representation in the absence of stimulus input enhances long-term encoding: a functional magnetic resonance imaging study of subsequent memory after a delayed match-to-sample task. *J Neurosci*, *24*, 11088–97. doi:10.1523/JNEUROSCI.3807-04.2004

Schon, K., Quiroz, Y. T., Hasselmo, M. E., & Stern, C. E. (2009). Greater working memory load results in greater medial temporal activity at retrieval. *Cereb Cortex*, *19*, 2561–71. doi:10.1093/cercor/bhp006

Schoo, L. A., van Zandvoort, M. J. E., Biessels, G. J., Kappelle, L. J., Postma, A., & de Haan, E. H. F. (2011). The posterior parietal paradox: Why do functional magnetic resonance imaging and lesion studies on episodic memory produce conflicting results? *Journal of Neuropsychology*, *5*(1), 15–38. doi:10.1348/174866410X504059

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery & Psychiatry*, *20*, 11–21.

Shallice, T., & Burgess, P. (1991). Higher-order cognitive impairments and frontal lobe lesions in man. *Frontal Lobe Function and Dysfunction*, 125–138.

Shallice, T., & Warrington, E. K. (1970). Independent functioning of verbal memory stores: a neuropsychological study. *Quarterly Journal of Experimental Psychology*, *22*, 261–73.

Shin, M. S., Lee, S., Seol, S. H., Lim, Y. J., Park, E. H., Sergeant, J. A., & Chung, C. (2009). Changes in neuropsychological functioning following temporal lobectomy in patients with temporal lobe epilepsy. *Neurological Research*, *31*, 692–701. doi:10.1179/174313209x389848

Shing, Y. L., Werkle-Bergner, M., Li, S.-C., & Lindenberger, U. (2008). Associative and strategic components of episodic memory: a life-span dissociation. *Journal of Experimental Psychology: General*, *137*(3), 495.

Shrager, Y., Levy, D. A., Hopkins, R. O., & Squire, L. R. (2008). Working memory and the organization of brain systems. *Journal of Neuroscience*, *28*, 4818–4822. doi:10.1523/Jneurosci.0710-08.2008

Silver, H., Goodman, C., & Bilker, W. B. (2012). Impairment in associative memory in healthy aging is distinct from that in other types of episodic memory. *Psychiatry Research*, *197*(1-2), 135–139. doi:10.1016/j.psychres.2012.01.025

Small, S. A., Schobel, S. A., Buxton, R. B., Witter, M. P., & Barnes, C. A. (2011). A pathophysiological framework of hippocampal dysfunction in ageing and disease. *Nature Reviews Neuroscience*, *12*, 585–601. doi:10.1038/Nrn3085

Smith, M. L., & Milner, B. (1981). The Role of the Right Hippocampus in the Recall of Spatial Location. *Neuropsychologia*, *19*, 781–&.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., ... Flitney, D. E. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*, *23*, S208.

Spencer, S. S. (2002). When should temporal-lobe epilepsy be treated surgically? *Lancet Neurology*, *1*, 375–382.

Spencer, W. D., & Raz, N. (1995). Differential effects of aging on memory for content and context: A meta-analysis. *Psychology and Aging*, *10*, 527–539.

Squire, L. R. (2004). Memory systems of the brain: A brief history and current perspective. *Neurobiology of Learning and Memory*, *82*(3), 171–177. doi:10.1016/j.nlm.2004.06.005

Squire, L. R. (2009a). Memory and brain systems: 1969-2009. *The Journal of Neuroscience*, *29*, 12711–6. doi:10.1523/JNEUROSCI.3575-09.2009

Squire, L. R. (2009b). The Legacy of Patient H.M. for Neuroscience. *Neuron*, *61*(1), 6–9. doi:10.1016/j.neuron.2008.12.023

Squire, L. R., Stark, C. E. L., & Clark, R. E. (2004). The medial temporal lobe. *Annu. Rev. Neurosci.*, *27*, 279–306.

Squire, L. R., & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science (New York, N.Y.)*, *253*(5026), 1380–1386.

Stark, C. E. L., Bayley, P. J., & Squire, L. R. (2002). Recognition memory for single items and for associations is similarly impaired following damage to the hippocampal region. *Learning & Memory*, *9*, 238–242. doi:10.1101/Lm.51802

Stepankova, K., Fenton, A. A., Pastalkova, E., Kalina, M., & Bohbot, W. D. (2004). Object-location memory impairment in patients with thermal lesions to the right or left hippocampus. *Neuropsychologia*, *42*, 1017–1028. doi:10.1016/j.neuropsychologia.2004.01.002

Sternberg, S. (1966). High-speed scanning in human memory. *Science*, *153*, 652–4.

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*, *18*, 643–661.

Tombaugh, T. N., & McIntyre, N. J. (1992). The mini-mental state examination: a comprehensive review. *Journal of the American Geriatrics Society*. Retrieved from http://psycnet.apa.org/psycinfo/1993-08048-001

Tudesco, I. D. S., Vaz, L. J., Mantoan, M. A. S., Belzunces, E., Noffs, M. H., Caboclo, L. O. S. F., ... Bueno, O. F. A. (2010). Assessment of working memory in patients with mesial temporal lobe epilepsy associated with unilateral hippocampal sclerosis. *Epilepsy & Behavior*, *18*, 223–228. doi:10.1016/j.yebeh.2010.04.021

Uttl, B. (2002). North American Adult Reading Test: age norms, reliability, and validity. *J Clin Exp Neuropsychol*, *24*, 1123–37. doi:10.1076/jcen.24.8.1123.8375

Van Asselen, M., Kessels, R. P. C., Wester, A. J., & Postma, A. (2005). Spatial working memory and contextual cueing in patients with Korsakoff amnesia. *J Clin Exp Neuropsychol*, *27*, 645–55. doi:10.1081/13803390490919281

Van der Elst, W., van Boxtel, M. P. J., van Breukelen, G. J. P., & Jolles, J. (2006). The Letter Digit Substitution Test: Normative Data for 1,858 Healthy Participants Aged 24–81 from the Maastricht Aging Study (MAAS): Influence of Age, Education, and Sex. *Journal of Clinical and Experimental Neuropsychology*, *28*(6), 998–1009. doi:10.1080/13803390591004428

Van der Elst, W., Van Boxtel, M. P., Van Breukelen, G. J., & Jolles, J. (2005). Rey's verbal learning test: normative data for 1855 healthy participants aged 24-81 years and the influence of age, sex, education, and mode of presentation. *Journal of the International Neuropsychological Society*, *11*(3), 290–302.

Van der Flier, W. M., & Scheltens, P. (2009). Alzheimer disease: hippocampal volume loss and Alzheimer disease progression. *Nat Rev Neurol*, *5*, 361–2. doi:10.1038/nrneurol.2009.94

Van der Werf, Y. D., Scheltens, P., Lindeboom, J., Witter, M. P., Uylings, H. B., & Jolles, J. (2003). Deficits of memory, executive functioning and attention following infarction in the thalamus; a study of 22 cases with localised lesions. *Neuropsychologia*, *41*, 1330–44.

Van Geldorp, B., Bergmann, H. C., Robertson, J., Wester, A. J., & Kessels, R. P. C. (2012). The interaction of working memory performance and episodic memory formation in patients with Korsakoff's amnesia. *Brain Research*, *1433*, 98–103. doi:10.1016/j.brainres.2011.11.036

Van Geldorp, B., Bouman, Z., Hendriks, M. P. H., & Kessels, R. P. C. (2014a). Different types of working memory binding in epilepsy patients with unilateral anterior temporal lobectomy. *Brain and Cognition*. doi:http://dx.doi.org/10.1016/j.bandc.2013.12.009

Van Geldorp, B., Bouman, Z., Hendriks, M. P. H., & Kessels, R. P. C. (2014b). Different types of working memory binding in epilepsy patients with unilateral anterior temporal lobectomy. *Brain and Cognition*, *85*, 231–238. doi:10.1016/j.bandc.2013.12.009

VarghaKhadem, F., Gadian, D. G., Watkins, K. E., Connelly, A., VanPaesschen, W., & Mishkin, M. (1997). Differential effects of early hippocampal pathology on episodic and semantic memory. *Science*, *277*, 376–380.

Verhage, R. (1964). *Intelligent en leeftijd*. Assen The Netherlands.

Visser, P. J., Krabbendam, L., Verhey, F. R., Hofman, P. A., Verhoeven, W. M., Tuinier, S., ... Jolles, J. (1999). Brain correlates of memory dysfunction in alcoholic Korsakoff's syndrome. *J Neurol Neurosurg Psychiatry*, *67*, 774–8.

Wagner, A. D., Shannon, B. J., Kahn, I., & Buckner, R. L. (2005). Parietal lobe contributions to episodic memory retrieval. *Trends in Cognitive Sciences*, *9*(9), 445–453. doi:10.1016/j.tics.2005.07.001

Warrington, E. K., James, M., & Thames Valley Test Company. (1991). *The visual object and space perception battery*. Bury St. Edmunds: Thames Valley Test Company.

Warrington, E. K., & Weiskrantz, L. (1970). Amnesic Syndrome - Consolidation or Retrieval. *Nature*, *228*, 628–630.

Wechsler, D. (1987). *WMS-R: Wechsler Memory Scale–Revised: manual*. Psychological Corporation San Antonio. Retrieved from http://www.getcited.org/pub/103239993

Wechsler, D. (1997). *Wechsler Adult Intelligence Scale-Third Edition*. San Antonio, TX: Psychological Corporation.

Wechsler, D. (2009). *Wechsler memory scale: WMS-IV ; technical and interpretive manual*. San Antonio, Tex. [u.a.: Pearson.

Wheeler, M. E., & Treisman, A. M. (2002). Binding in short-term visual memory. *Journal of Experimental Psychology-General*, *131*, 48–64. doi:10.1037//0096-3445.131.1.48

Woolrich, M. W., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T., ... Smith, S. M. (2009). Bayesian analysis of neuroimaging data in FSL. *Neuroimage*, *45*(1 Suppl), S173–S186.

Zola-Morgan, S., Squire, L. R., & Amaral, D. G. (1986). Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *6*(10), 2950–2967.

Nederlandse samenvatting

Achtergrond

Het geheugen is één van de meest onderzochte cognitieve functies. Onderzoek naar het geheugen is relevant voor meerdere patiëntgroepen. De populatie ouderen met geheugenproblemen groeit. Het World Alzheimer Report van 2013 gaf bijvoorbeeld aan dat het aantal mensen met dementie, waarbij geheugenproblemen prominent zijn, in het jaar 2030 verdubbeld zal zijn. Het is daarom niet alleen vanuit theoretisch perspectief een interessant onderzoeksgebied, maar ook vanuit klinisch perspectief zeer relevant.

Binnen de cognitieve psychologie wordt onderscheid gemaakt tussen vele verschillende geheugensystemen. Het onderzoek in dit proefschrift richt zich op twee van deze deelsystemen: het werkgeheugen en het episodisch geheugen. Werkgeheugen gebruiken we wanneer informatie voor een korte tijd vastgehouden moet worden om er iets mee te doen (bijvoorbeeld bij hoofdrekenen of het kortdurend onthouden van een telefoonnummer). De duur van het werkgeheugen is enkele seconden en de capaciteit is beperkt tot 5-7 eenheden. Het episodisch geheugen is onderdeel van het langetermijngeheugen en betreft de herinneringen voor specifieke gebeurtenissen (bijvoorbeeld de laatste vakantie). De duur van het langetermijngeheugen varieert van minuten tot decennia, en de capaciteit is onbeperkt. Er zijn veel hersengebieden betrokken bij het geheugen. Traditioneel wordt er vanuit gegaan dat voor het werkgeheugen vooral gebieden in de frontaalkwab en de pariëtale schors van de hersenen nodig zijn. Voor het episodisch geheugen zijn met name gebieden in de mediale temporaalkwab betrokken, waaronder de hippocampus. Er is dus sprake van een duidelijke scheiding tussen de geheugensystemen en hun representatie in de hersenen.

Recente studies tonen echter met behulp van beeldvormende technieken (zoals functionele MRI) aan dat er activiteit in de mediale temporaalkwab (vooral in de hippocampus) optreedt tijdens het uitvoeren van werkgeheugentaken. Dit lijkt vooral het geval te zijn wanneer informatie geassocieerd moet worden, ook wel *binding* genoemd. Daarnaast zijn er studies bij patiënten met amnesie die werkgeheugenproblemen aantonen. Amnesie is een langetermijngeheugenstoornis, die meestal gepaard gaat met beschadigingen in de mediale temporaalkwab. Deze bevindingen lijken in tegenspraak met de traditionele scheiding tussen de geheugensystemen, waarbij het werkgeheugen doorgaans gezien wordt als een geheugensysteem dat onafhankelijk van de mediale temporaalkwab opereert.

Er zijn verschillende hypotheses over de rol van de mediale temporaalkwab in het werkgeheugen. Ten eerste is het mogelijk dat de mediale temporaalkwab belangrijk is voor het onthouden van associatieve informatie in het algemeen. Dat wil zeggen: onafhankelijk van of de informatie voor korte of lange termijn

onthouden moet worden. Ten tweede is het mogelijk dat de hersenactiviteit in de mediale temporaalkwab die gezien wordt tijdens werkgeheugentaken 'toevallige' processen zijn die zorgen voor de opslag van de informatie in het langetermijngeheugen, maar niet noodzakelijk zijn voor het werkgeheugen an sich. Ten derde is het mogelijk dat de mediale temporaalkwab pas betrokken wordt bij een taak wanneer de capaciteit van het werkgeheugen overschreden wordt. Langetermijngeheugenprocessen kunnen de prestatie op de taak dan ondersteunen, bijvoorbeeld wanneer er veel onthouden moet worden. Dit is de zogeheten werkgeheugen-overload hypothese.

Deze drie hypotheses heb ik op empirische wijze onderzocht. Aan mijn onderzoek werkten verschillende patiëntgroepen mee die door hun aandoening een beschadigde of disfunctionerende temporaalkwab hebben en langetermijngeheugenstoornissen vertonen. Hiermee onderzocht ik of de strikte scheiding tussen werkgeheugen en langetermijngeheugen nog wel te verantwoorden is. Ook onderzocht ik welke rol de temporaalkwab speelt in het werkgeheugen, en heb ik het geheugen in het kader van gezonde veroudering onderzocht. In de hierop volgende alinea's geef ik een samenvatting van ieder hoofdstuk uit dit proefschrift. Daarna bespreek ik de resultaten in het licht van de drie bovengenoemde hypotheses.

Samenvatting

In hoofdstuk 2 hebben patiënten in een vroeg stadium van de ziekte van Alzheimer een werkgeheugen-bindingtaak uitgevoerd. De resultaten laten zien dat er een werkgeheugenprobleem is. Dit probleem neemt toe met een toenemend aantal items dat onthouden moest worden.

Hoofdstuk 3 beschrijft patiënten die een herseninfarct of -bloeding gehad hebben. Dergelijke aandoeningen betreffen meestal andere hersengebieden dan de temporaalkwab. Deze patiënten lieten geen problemen zien in werkgeheugenbinding en in het langetermijngeheugen.

Bij de patiënten die in hoofdstuk 4 beschreven zijn, is operatief een deel van de mediale temporaalkwab verwijderd ter behandeling van hun ernstige epilepsie. Deze patiënten hebben dus aan één kant selectieve beschadigingen in de mediale temporaalkwab. In dit hoofdstuk zijn verschillende vormen van *binding* met elkaar vergeleken. Wanneer twee losstaande items of eigenschappen verbonden moeten worden, spreken we van *relationele binding*. Wanneer geïntegreerde eigenschappen van een object geassocieerd moeten worden (bijvoorbeeld de kleur van een object), gebruiken we de term *conjunctieve binding*. De geopereerde patiënten bleken problemen te hebben met relationele binding (object-object-*binding* of object-locatie-*binding*), maar niet met conjunctieve binding (object-kleur-*binding*). Het werkgeheugen voor losse informatie was alleen beperkt wanneer deze informatie voor langere tijd onthouden moest worden (dat wil zeggen, na een langere delay-

periode). Het idee van de werkgeheugen-overload lijkt het beste bij de resultaten te passen: de mediale temporaalkwab wordt betrokken bij een taak wanneer de capaciteit van het werkgeheugen niet voldoende is om de taak te kunnen uitvoeren. Dit is het geval bij *binding* en bij lange delay-periodes, waardoor patiënten met langetermijngeheugenstoornissen slecht presteren op dergelijke werkgeheugentaken.

In hoofdstuk 5 en 6 onderzocht ik de hypothese dat de geobserveerde hersenactiviteit in de temporaalkwab het resultaat is van langetermijngeheugenprocessen die tijdens de taak in werking zijn. Patiënten met het syndroom van Korsakov voerden een taak uit waarbij ze combinaties van gezichten en huizen moesten onthouden voor ofwel een korte (3 seconden) ofwel een lange (6 seconden) delay-periode (hoofdstuk 5). We verwachtten dat een langere delay-periode tot meer langetermijngeheugenprocessen zou leiden: gedurende een langere periode kan de informatie mentaal herhaald worden (*rehearsal*) en zo overgedragen worden naar het langetermijngeheugen. Mogelijk wordt de informatie hierdoor beter onthouden op lange termijn. Dit vonden we echter niet terug in de resultaten.

Ook in hoofdstuk 6 vonden we geen bewijs voor het idee dat langere delay-periodes zorgen voor een betere herinnering op lange termijn. Dit bleek noch bij gezonde ouderen noch bij jongeren het geval. Patiënten met de ziekte van Alzheimer toonden eenzelfde prestatiepatroon als de patiënten met het syndroom van Korsakov. Het lijkt erop dat deze werkgeheugentaak zorgt voor een overschrijding van de werkgeheugencapaciteit door het gebruik van *binding*. Kortom, langetermijngeheugenprocessen kunnen worden gebruikt om de uitvoering van de taak te ondersteunen, maar patiënten met amnesie kunnen hier geen gebruik van maken. Waarschijnlijk presteren zij daarom aanzienlijk slechter op deze taak dan gezonde controledeelnemers.

hoofdstuk 7 wordt wederom een onderzoek beschreven met een werkgeheugentaak bij een groep patiënten in de vroege fase van de ziekte van Alzheimer. Ook hier was sprake van een werkgeheugenprobleem, hoewel dit probleem niet sterker werd met een toenemend aantal te onthouden items. De hersenscans die beschikbaar waren voor deze patiënten toonden een relatie tussen de prestatie op de werkgeheugentaak en de mate waarin de hippocampus (onderdeel van de mediale temporaalkwab) aangetast is. De resultaten van dit onderzoek wijzen erop dat de toenemende hoeveelheid informatie niet direct voor grotere problemen zorgt bij de patiënten. Het lijkt er eerder op dat de volgorde van de items een rol speelt: latere items verstoren (interfereren met) de herinnering van eerder getoonde informatie.

Om dit interfererende effect op werkgeheugenbinding nader te onderzoeken, heb ik in hoofdstuk 8 een interferentietaak toegevoegd aan een werkgeheugentaak waarbij verschillende soorten *binding* onderzocht werden. Het bleek dat *relationele binding* gevoeliger is voor interferentie dan *conjunctieve binding*. Dit wijst erop dat *relationele binding* meer capaciteit vereist dan *conjunctieve binding*.

De rol van de mediale temporaalkwab in het werkgeheugen

De studies in het huidige proefschrift lijken te bevestigen dat disfuncties van de mediale temporaalkwab leiden tot problemen bij het uitvoeren van werkgeheugentaken, waarbij gedurende een korte periode informatie moet worden vastgehouden. Van groter belang is echter de vraag *waarom* dit gebied een rol speelt bij de uitvoering van dergelijke taken. Zoals eerder besproken zijn er drie hypotheses die de betrokkenheid van de mediale temporaalkwab proberen te verklaren. De resultaten van mijn onderzoek kunnen in het licht van die hypotheses worden geïnterpreteerd. Hoewel de meeste onderzoeken die beschreven zijn in dit proefschrift erop wijzen dat amnesiepatiënten problemen hebben met werkgeheugenbinding, is dit onvoldoende bewijs voor de stelling dat het enkel het relationele aspect van de taak is dat resulteert in de betrokkenheid van de mediale temporaalkwab. Deze hypothese is te globaal om de resultaten te kunnen verklaren.

Ook de tweede hypothese, die stelt dat opslagprocessen voor het langetermijngeheugen plaatsvinden tijdens werkgeheugentaken, vindt onvoldoende steun in de resultaten van de onderzoeken die beschreven staan in de voorgaande hoofdstukken. Er werd namelijk in hoofdstuk 5 en 6 geen bewijs gevonden voor het idee dat deze langetermijngeheugenprocessen resulteren in betere geheugenprestaties op langere termijn.

De theorie die stelt dat de overschrijding van de werkgeheugencapaciteit zorgt voor de betrokkenheid van de mediale temporaalkwab vindt de meeste steun in de beschreven onderzoeken. Wanneer associaties onthouden moeten worden of wanneer de informatie gedurende langere delay-periodes onthouden moet worden, is de capaciteit van het werkgeheugen niet langer toereikend om de taak te volbrengen. In dit geval worden langetermijnprocessen ingezet om de prestatie op de taak te ondersteunen. Patiënten met een disfunctionerende mediale temporaalkwab kunnen geen gebruik maken van deze ondersteuning en falen daardoor bij dergelijke werkgeheugentaken.

Samenvattend kan gesteld worden dat de meeste resultaten uit dit proefschrift passen bij de hypothese van werkgeheugen-overload. De werkgeheugencapaciteit kan op verschillende manieren overschreden worden. Dit kan enerzijds gebeuren door de associatieve component (*binding*) van de taak, waardoor niet alleen de informatie zelf, maar ook de associatie daartussen onthouden moet worden. Anderzijds kan een langere delay-periode ook leiden tot het overschrijden van de werkgeheugencapaciteit; langere delays geven meer ruimte voor *rehearsal* en het toepassen van strategieën (zoals het vormen van associaties met bestaande kennis). De langetermijngeheugenprocessen die vervolgens gebruikt worden om de taakprestatie te ondersteunen, leiden echter niet noodzakelijk tot verbeterde prestatie op de lange termijn.

De resultaten uit dit proefschrift zijn niet alleen van belang voor de wetenschap en haar theorieën over het geheugen en de representatie ervan in de hersenen. Ook de klinische praktijk kan gebruik maken van de verworven kennis. Over het algemeen wordt er weinig tijd besteed aan het werkgeheugen en wordt volstaan met een cijferreeksentaak wanneer men patiënten onderzoekt met (episodische) geheugenklachten. De meeste standaard werkgeheugentests tonen echter weinig problemen aan bij deze patiënten. Complexere werkgeheugentaken zijn nodig om een werkgeheugenprobleem aan te tonen bij patiënten met een disfunctionerende of beschadigde mediale temporaalkwab. De invloed van werkgeheugenproblematiek voor het algeheel functioneren werkt ook door in mogelijke behandelingen, zoals te zien is bij onder andere de Cogmed werkgeheugentraining.

Tot besluit

De studies in het huidige proefschrift laten zien dat er meer aandacht geschonken moet worden aan de sterke relatie tussen het werkgeheugen en het langetermijngeheugen, aangezien deze twee geheugensystemen niet gemakkelijk te isoleren zijn. Er zijn altijd meerdere processen die de prestatie op een taak ondersteunen. Voor de klinische praktijk betekent dit dat er meer aandacht geschonken moet worden aan de mogelijke aanwezigheid van werkgeheugenproblemen wanneer patiënten met (episodische) geheugenklachten worden onderzocht.

Dankwoord

Gedurende de afgelopen viereneenhalf jaar heb ik met veel fijne mensen mogen samenwerken, zonder wie dit proefschrift er beslist niet was gekomen.

Allereerst wil ik mijn promotor en dagelijks begeleider Prof. Dr. Roy Kessels bedanken. Beste Roy, met jouw actieve inzet en betrokken rol heb je ervoor gezorgd dat mijn project op rolletjes liep. Je gooide me vanaf het begin in het diepe, maar ik heb nooit het gevoel gehad dat je me liet zwemmen. Hoewel je nooit veel tijd hebt, maakte je altijd tijd voor me vrij. Maar zoals Heiko ook al schreef in zijn dankwoord: we vreesden altijd een beetje voor de momenten dat jij vrolijk onze kamer binnen kwam lopen en op luchtige wijze de rottigste vragen stelde die je als aio gesteld kunnen worden ('Is de dataverzameling al compleet? Heb je het artikel al ingediend? Is de inleiding voor je proefschrift al klaar?'). Je optimisme is niet te stuiten en werkt aanstekelijk. Kort gezegd hebben jouw enthousiasme, praktische hulp, laagdrempeligheid en je vertrouwen geholpen om mijn promotie een heel leerzame en prettige periode te laten zijn.

Ik wil de leden van de manuscriptcommissie bedanken voor het nauwgezet lezen van mijn manuscript. De twee heren uit de commissie wil ik daarbij extra bedanken. Martijn, jij hebt als gedreven en betrokken begeleider van mijn masterscriptie mijn enthousiasme voor het patiëntgebonden onderzoek flink aangezwengeld. Jos, bedankt dat je me de mogelijkheid biedt om me verder te ontwikkelen in de klinische kant van de neuropsychologie.

Alle instellingen en mensen met wie ik samengewerkt heb om de data voor dit proefschrift te verzamelen wil ik hartelijk bedanken. Van de afdeling Geriatrie van het UMC St. Radboud zijn dat Marcel Olde-Rikkert en mijn MRI-analyse-heldin Olga Meulenbroek, maar ook Ilja Klabbers, Saskia Oosterveld, Maartje de Werd, Sondra Roelofs en Lonneke Staargaard, omdat jullie het mogelijk maakten om mijn onderzoek mee te laten draaien op de afdeling. Van de afdeling Neurologie en Neurochirurgie van het UMC Utrecht wil ik Geert Jan Biessels bedanken voor de samenwerking. Sophie Heringa, bedankt voor het (ontzettend vaak) afnemen van mijn taak. Bij de Korsakovkliniek van het Vincent van Gogh in Venray hebben Arie Wester en Johanna Robertson ervoor gezorgd dat het onderzoek in goede banen werd geleid en in het Elkerliek ziekenhuis te Helmond waren dat Ilse van Tilborg en Elke Konings. Voor de studie die uitgevoerd is bij Kempenhaeghe wil ik Marc Hendriks en Zita Bouman bedanken. Zita, je hebt ongekend hard gewerkt voor dit onderzoek en ik ben erg blij dat je na je scriptieonderzoek mijn collega-aio bent geworden. Also, a special thanks to the people I had the pleasure to collaborate

with within the UK: Prof. Masud Husain and Nikos Gorgoraptis from UCL and Mario Parra from the University of Edinburgh. Ook de masterstudenten Maaike Gaastra, Maartje Hutten en Hans de Voer, en bachelorstudenten Karina Burger, Marloes de Jonge, Lieke van Lieshout en Iris Wensink wil ik bedanken voor hun bijdrage aan de dataverzameling voor dit proefschrift.

Mijn collega's van de afdeling Neuro- en Revalidatiepsychologie wil ik niet alleen bedanken voor hun inhoudelijke bijdrage aan mijn promotietraject, maar ook voor hun betrokkenheid en gezelligheid. Door jullie ben ik altijd met veel plezier naar mijn werk gegaan. In dit verband wil ik in het bijzonder Saskia van Uum bedanken voor haar nimmer aflatende behulpzaamheid, goede adviezen, opgeruimd humeur en persoonlijke interesse. En natuurlijk voor het op peil houden van mijn bloeddruk tijdens mijn zwangerschap met behulp van de goed gevulde droppot. Gedurende de afgelopen vier jaar heeft dit unieke clubje collega-aio's enorm bijgedragen aan mijn werkplezier: Dirk Bertens, Zita Bouman, Jessica van Damme en kamergenoten/paranimfen Heiko Bergmann en Evelien Barendse. Op jullie aanwezigheid en morele steun kon ik altijd rekenen. Jullie hadden (al dan niet tijdens de koffiepauze) goede adviezen over o.a. statistische vraagstukken, het geven van werkgroepen, hoe om te gaan met studenten (van ieder kaliber), ingewikkelde commentaren van reviewers of immer te krappe tijdsplanningen. Maar vooral ook alle niet werk-gerelateerde gesprekken en het (bijna) dagelijkse hoogtepuntje van 'het spreekwoord van de dag' zorgden voor significante stress-reductie. Heel veel dank hiervoor en ik hoop dat we elkaar niet uit het oog verliezen.

Zonder de medewerking van alle patiënten en controledeelnemers, had dit proefschrift nooit tot stand kunnen komen. Daarom wil ik alle mensen die hebben deelgenomen aan mijn onderzoek hartelijk bedanken. Jullie interesse in geheugenproblematiek en de enorme inzet die jullie toonden tijdens het uitvoeren van die lastige en soms saaie tests heeft me altijd erg vrolijk gestemd. Jullie herinnerden me er steeds aan waarom ik dit onderzoek doe en waarom ik zo graag met (oudere) mensen werk.

Tot slot wil ik de mensen bedanken die inhoudelijk eigenlijk niets met mijn werk te maken hadden, maar toch erg belangrijk voor me zijn geweest. Dank aan alle vrienden die regelmatig voor de broodnodige ontspanning zorgden, en dan vooral dank aan 'BFF' Esmeralda Bierings. Jouw nuchtere blik op zaken die voor mij stressfactoren waren en je aanpakkersmentaliteit hebben me vaak geholpen om mezelf over mijn stress en onzekerheid heen te zetten. Broer(tje) Roy: met je humor heb je vaker dan je zelf misschien denkt mijn stressniveau even laten zakken. Mijn

ouders, Nico en Ada, bedankt dat jullie me zelfvertrouwen hebben gegeven, zodat ik durf te doen wat ik graag wil doen. Jullie staan achter iedere keuze die ik maak en staan altijd voor me klaar. Het komt grotendeels door jullie vertrouwen dat ik ben gekomen waar ik nu ben; dat ik eindelijk ga promoveren van zuster Bonnie naar dr. Bonnie. Frank, jouw humor, relativeringsvermogen en je oplossingsgerichte instelling zijn een grote steun voor me geweest de afgelopen jaren. Je geeft me op de goede momenten een dikke knuffel of een flinke schop onder mijn hol. Ik ben trots op jou, op ons en op onze kleine Siem.

Bonnie

Curriculum vitae

Bonnie van Geldorp was born on May 30th 1986 in Limmen. After completing the VWO (Higher Scientific Secondary Education) at the Jac. P. Thijsse College in Castricum, she studied psychology at the Vrije Universiteit in Amsterdam, majoring in Cognitive Neuropsychology. She did her master internship in Mark Gluck's memory lab at Rutgers University, Newark, USA, with a thesis on implicit category learning in Parkinson´s Disease. She obtained her research master diploma with distinction (*cum laude*) in 2009.

After graduating, she started working as a PhD student at the Radboud Universiteit Nijmegen, with Roy Kessels as promotor. In her research, she focused on the relationship between working memory and long-term memory, working with several patient populations and healthy older adults.

Since February 2014, she started working as a trainee at the Vincent van Gogh Institute for Psychiatry in Venray. Here, she aims to obtain the qualifications in order to work as a psychologist. In the future, she prefers to combine patient care with clinical research.

Donders Graduate School for Cognitive Neuroscience Series

1. Van Aalderen-Smeets, S.I. (2007). *Neural dynamics of visual selection.* Maastricht University, Maastricht, the Netherlands.
2. Schoffelen, J.M. (2007). *Neuronal communication through coherence in the human motor system.* Radboud University Nijmegen, Nijmegen, the Netherlands.
3. De Lange, F.P. (2008). *Neural mechanisms of motor imagery.* Radboud University Nijmegen, Nijmegen, the Netherlands.
4. Grol, M.J. (2008). *Parieto-frontal circuitry in visuomotor control.* Utrecht University, Utrecht, the Netherlands.
5. Bauer, M. (2008). *Functional roles of rhythmic neuronal activity in the human visual and somatosensory system.* Radboud University Nijmegen, Nijmegen, the Netherlands.
6. Mazaheri, A. (2008). *The influence of ongoing oscillatory brain activity on evoked responses and behaviour.* Radboud University Nijmegen, Nijmegen, the Netherlands.
7. Hooijmans, C.R. (2008). *Impact of nutritional lipids and vascular factors in Alzheimer's disease.* Radboud University Nijmegen, Nijmegen, the Netherlands.
8. Gaszner, B. (2008). *Plastic responses to stress by the rodent urocortinergic Edinger-Westphal nucleus.* Radboud University Nijmegen, Nijmegen, the Netherlands.
9. Willems, R.M. (2009). *Neural reflections of meaning in gesture, language and action.* Radboud University Nijmegen, Nijmegen, the Netherlands.
10. Van Pelt, S. (2009). *Dynamic neural representations of human visuomotor space.* Radboud University Nijmegen, Nijmegen, the Netherlands.
11. Lommertzen, J. (2009). *Visuomotor coupling at different levels of complexity.* Radboud University Nijmegen, Nijmegen, the Netherlands.
12. Poljac, E. (2009). *Dynamics of cognitive control in task switching: Looking beyond the switch cost.* Radboud University Nijmegen, Nijmegen, the Netherlands.
13. Poser, B.A. (2009). *Techniques for BOLD and blood volume weighted fMRI.* Radboud University Nijmegen, Nijmegen, the Netherlands.
14. Baggio, G. (2009). *Semantics and the electrophysiology of meaning. Tense, aspect, event structure.* Radboud University Nijmegen, Nijmegen, the Netherlands.
15. Van Wingen, G.A. (2009). *Biological determinants of amygdala functioning.* Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
16. Bakker, M. (2009). *Supraspinal control of walking: Lessons from motor imagery.* Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
17. Aarts, E. (2009). *Resisting temptation: The role of the anterior cingulate cortex in adjusting cognitive control.* Radboud University Nijmegen, Nijmegen, the Netherlands.
18. Prinz, S. (2009). *Waterbath stunning of chickens – Effects of electrical parameters on the electroencephalogram and physical reflexes of broilers.* Radboud University Nijmegen, Nijmegen, the Netherlands.
19. Knippenberg, J.M.J. (2009). *The N150 of the Auditory Evoked Potential from the rat amygdala: In search for its functional significance.* Radboud University Nijmegen, Nijmegen, the Netherlands.
20. Dumont, G.J.H. (2009). *Cognitive and physiological effects of 3,4-methylenedioxymethamphetamine (MDMA or 'ecstasy') in combination with alcohol or cannabis in humans.* Radboud University Nijmegen, Nijmegen, the Netherlands.
21. Pijnacker, J. (2010). *Defeasible inference in autism: A behavioral and electrophysiogical approach.* Radboud University Nijmegen, Nijmegen, the Netherlands.
22. De Vrijer, M. (2010). *Multisensory integration in spatial orientation.* Radboud University Nijmegen, Nijmegen, the Netherlands.
23. Vergeer, M. (2010). *Perceptual visibility and appearance: Effects of color and form.* Radboud University Nijmegen, Nijmegen, the Netherlands.
24. Levy, J. (2010). *In cerebro unveiling unconscious mechanisms during reading.* Radboud University Nijmegen, Nijmegen, the Netherlands.

25. Treder, M. S. (2010). *Symmetry in (inter)action*. Radboud University Nijmegen, Nijmegen, the Netherlands.
26. Horlings C.G.C. (2010). *A weak balance: Balance and falls in patients with neuromuscular disorders.* Radboud University Nijmegen, Nijmegen, the Netherlands.
27. Snaphaan, L.J.A.E. (2010). *Epidemiology of post-stroke behavioural consequences.* Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
28. Dado – Van Beek, H.E.A. (2010). *The regulation of cerebral perfusion in patients with Alzheimer's disease.* Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
29. Derks, N.M. (2010). *The role of the non-preganglionic Edinger-Westphal nucleus in sex-dependent stress adaptation in rodents.* Radboud University Nijmegen, Nijmegen, the Netherlands.
30. Wyczesany, M. (2010). *Covariation of mood and brain activity. Integration of subjective self-report data with quantitative EEG measures.* Radboud University Nijmegen, Nijmegen, the Netherlands.
31. Beurze S.M. (2010). *Cortical mechanisms for reach planning.* Radboud University Nijmegen, Nijmegen, the Netherlands.
32. Van Dijk, J.P. (2010). *On the Number of Motor Units.* Radboud University Nijmegen, Nijmegen, the Netherlands.
33. Lapatki, B.G. (2010). *The Facial Musculature - Characterization at a Motor Unit Level.* Radboud University Nijmegen, Nijmegen, the Netherlands.
34. Kok, P. (2010). *Word order and verb inflection in agrammatic sentence production.* Radboud University Nijmegen, Nijmegen, the Netherlands.
35. van Elk, M. (2010). *Action semantics: Functional and neural dynamics.* Radboud University Nijmegen, Nijmegen, the Netherlands.
36. Majdandzic, J. (2010). *Cerebral mechanisms of processing action goals in self and others.* Radboud University Nijmegen, Nijmegen, the Netherlands.
37. Snijders, T.M. (2010). *More than words - Neural and genetic dynamics of syntactic unification.* Radboud University Nijmegen, Nijmegen, the Netherlands.
38. Grootens, K.P. (2010). *Cognitive dysfunction and effects of antipsychotics in schizophrenia and borderline personality disorder.* Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
39. Nieuwenhuis, I.L.C. (2010). *Memory consolidation: A process of integration – Converging evidence from MEG, fMRI and behavior.* Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
40. Menenti, L.M.E. (2010). *The right language: Differential hemispheric contributions to language production and comprehension in context.* Radboud University Nijmegen, Nijmegen, the Netherlands.
41. Van Dijk, H.P. (2010). *The state of the brain, how alpha oscillations shape behaviour and event related responses.* Radboud University Nijmegen, Nijmegen, the Netherlands.
42. Meulenbroek, O.V. (2010). *Neural correlates of episodic memory in healthy aging and Alzheimer's disease.* Radboud University Nijmegen, Nijmegen, the Netherlands.
43. Oude Nijhuis, L.B. (2010). *Modulation of human balance reactions.* Radboud University Nijmegen, Nijmegen, the Netherlands.
44. Qin, S. (2010). *Adaptive memory: Imaging medial temporal and prefrontal memory systems.* Radboud University Nijmegen, Nijmegen, the Netherlands.
45. Timmer, N.M. (2011). *The interaction of heparan sulfate proteoglycans with the amyloid protein.* Radboud University Nijmegen, Nijmegen, the Netherlands.
46. Crajé, C. (2011). *(A)typical motor planning and motor imagery.* Radboud University Nijmegen, Nijmegen, the Netherlands.
47. Van Grootel, T.J. (2011). *On the role of eye and head position in spatial localisation behaviour.* Radboud University Nijmegen, Nijmegen, the Netherlands.
48. Lamers, M.J.M. (2011). *Levels of selective attention in action planning.* Radboud University Nijmegen, Nijmegen, the Netherlands.
49. Van der Werf, J. (2011). *Cortical oscillatory activity in human visuomotor integration*. Radboud University Nijmegen, Nijmegen, the Netherlands.
50. Scheeringa, R. (2011). *On the relation between oscillatory EEG activity and the BOLD signal.* Radboud University Nijmegen, Nijmegen, the Netherlands.

51. Bögels, S. (2011). *The role of prosody in language comprehension: When prosodic breaks and pitch accents come into play.* Radboud University Nijmegen, Nijmegen, the Netherlands.
52. Ossewaarde, L. (2011). *The mood cycle: Hormonal influences on the female brain.* Radboud University Nijmegen, Nijmegen, the Netherlands.
53. Kuribara, M. (2011). *Environment-induced activation and growth of pituitary melanotrope cells of Xenopus laevis.* Radboud University Nijmegen, Nijmegen, the Netherlands.
54. Helmich, R.C.G. (2011). *Cerebral reorganization in Parkinson's disease.* Radboud University Nijmegen, Nijmegen, the Netherlands.
55. Boelen, D. (2011). *Order out of chaos? Assessment and treatment of executive disorders in brain-injured patients.* Radboud University Nijmegen, Nijmegen, the Netherlands.
56. Koopmans, P.J. (2011). *fMRI of cortical layers.* Radboud University Nijmegen, Nijmegen, the Netherlands.
57. van der Linden, M.H. (2011). *Experience-based cortical plasticity in object category representation.* Radboud University Nijmegen, Nijmegen, the Netherlands.
58. Kleine, B.U. (2011). *Motor unit discharges - Physiological and diagnostic studies in ALS.* Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
59. Paulus, M. (2011). *Development of action perception: Neurocognitive mechanisms underlying children's processing of others' actions.* Radboud University Nijmegen, Nijmegen, the Netherlands.
60. Tieleman, A.A. (2011). *Myotonic dystrophy type 2. A newly diagnosed disease in the Netherlands.* Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
61. Van Leeuwen, T.M. (2011). *'How one can see what is not there': Neural mechanisms of grapheme-colour synaesthesia.* Radboud University Nijmegen, Nijmegen, the Netherlands.
62. Van Tilborg, I.A.D.A. (2011). *Procedural learning in cognitively impaired patients and its application in clinical practice.* Radboud University Nijmegen, Nijmegen, the Netherlands.
63. Bruinsma, I.B. (2011). *Amyloidogenic proteins in Alzheimer's disease and Parkinson's disease: Interaction with chaperones and inflammation.* Radboud University Nijmegen, Nijmegen, the Netherlands.
64. Voermans, N. (2011). *Neuromuscular features of Ehlers-Danlos syndrome and Marfan syndrome; expanding the phenotype of inherited connective tissue disorders and investigating the role of the extracellular matrix in muscle.* Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
65. Reelick, M. (2011). *One step at a time. Disentangling the complexity of preventing falls in frail older persons.* Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
66. Buur, P.F. (2011). *Imaging in motion. Applications of multi-echo fMRI.* Radboud University Nijmegen, Nijmegen, the Netherlands.
67. Schaefer, R.S. (2011). *Measuring the mind's ear: EEG of music imagery.* Radboud University Nijmegen, Nijmegen, the Netherlands.
68. Xu, L. (2011). *The non-preganglionic Edinger-Westphal nucleus: An integration center for energy balance and stress adaptation.* Radboud University Nijmegen, Nijmegen, the Netherlands.
69. Schellekens, A.F.A. (2011). *Gene-environment interaction and intermediate phenotypes in alcohol dependence.* Radboud University Nijmegen, Nijmegen, the Netherlands.
70. Van Marle, H.J.F. (2011). *The amygdala on alert: A neuroimaging investigation into amygdala function during acute stress and its aftermath.* Radboud University Nijmegen, Nijmegen, the Netherlands.
71. De Laat, K.F. (2011). *Motor performance in individuals with cerebral small vessel disease: An MRI study.* Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
72. Mädebach, A. (2011). *Lexical access in speaking: Studies on lexical selection and cascading activation.* Radboud University Nijmegen, Nijmegen, the Netherlands.
73. Poelmans, G.J.V. (2011). *Genes and protein networks for neurodevelopmental disorders.* Radboud University Nijmegen, Nijmegen, the Netherlands.
74. Van Norden, A.G.W. (2011). *Cognitive function in elderly individuals with cerebral small vessel disease. An MRI study.* Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
75. Jansen, E.J.R. (2011). *New insights into V-ATPase functioning: the role of its accessory subunit Ac45 and a novel brain-specific Ac45 paralog.* Radboud University Nijmegen, Nijmegen, the Netherlands.
76. Haaxma, C.A. (2011). *New perspectives on preclinical and early stage Parkinson's disease.* Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.

77. Haegens, S. (2012). *On the functional role of oscillatory neuronal activity in the somatosensory system.* Radboud University Nijmegen, Nijmegen, the Netherlands.
78. van Barneveld, D.C.P.B.M. (2012). *Integration of exteroceptive and interoceptive cues in spatial localization.* Radboud University Nijmegen, Nijmegen, the Netherlands.
79. Spies, P.E. (2012). *The reflection of Alzheimer disease in CSF.* Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
80. Helle, M. (2012). *Artery-specific perfusion measurements in the cerebral vasculature by magnetic resonance imaging.* Radboud University Nijmegen, Nijmegen, the Netherlands.
81. Egetemeir, J. (2012). *Neural correlates of real-life joint action.* Radboud University Nijmegen, Nijmegen, the Netherlands.
82. Janssen, L. (2012). *Planning and execution of (bi)manual grasping.* Radboud University Nijmegen, Nijmegen, the Netherlands.
83. Vermeer, S. (2012). *Clinical and genetic characterisation of autosomal recessive cerebellar ataxias.* Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
84. Vrins, S. (2012). *Shaping object boundaries: Contextual effects in infants and adults.* Radboud University Nijmegen, Nijmegen, the Netherlands.
85. Weber, K.M. (2012). *The language learning brain: Evidence from second language and bilingual studies of syntactic processing.* Radboud University Nijmegen, Nijmegen, the Netherlands.
86. Verhagen, L. (2012). *How to grasp a ripe tomato.* Utrecht University, Utrecht, the Netherlands.
87. Nonkes, L.J.P. (2012). *Serotonin transporter gene variance causes individual differences in rat behaviour: For better and for worse.* Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
88. Joosten-Weyn Banningh, L.W.A. (2012). *Learning to live with Mild Cognitive Impairment: development and evaluation of a psychological intervention for patients with Mild Cognitive Impairment and their significant others.* Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
89. Xiang, HD. (2012). *The language networks of the brain.* Radboud University Nijmegen, Nijmegen, the Netherlands.
90. Snijders, A.H. (2012). *Tackling freezing of gait in Parkinson's disease.* Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
91. Rouwette, T.P.H. (2012). *Neuropathic pain and the brain - Differential involvement of corticotropin-releasing factor and urocortin 1 in acute and chronic pain processing.* Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
92. Van de Meerendonk, N. (2012). *States of indecision in the brain: Electrophysiological and hemodynamic reflections of monitoring in visual language perception.* Radboud University Nijmegen, Nijmegen, the Netherlands.
93. Sterrenburg, A. (2012). *The stress response of forebrain and midbrain regions: Neuropeptides, sex-specificity and epigenetics.* Radboud University Nijmegen, Nijmegen, The Netherlands.
94. Uithol, S. (2012). *Representing action and intention.* Radboud University Nijmegen, Nijmegen, The Netherlands.
95. Van Dam, W.O. (2012). *On the specificity and flexibility of embodied lexical-semantic representations.* Radboud University Nijmegen, Nijmegen, The Netherlands.
96. Slats, D. (2012). *CSF biomarkers of Alzheimer's disease: Serial sampling analysis and the study of circadian rhythmicity.* Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
97. Van Nuenen, B.F.L. (2012). *Cerebral reorganization in premotor parkinsonism.* Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
98. van Schouwenburg, M.R. (2012). *Fronto-striatal mechanisms of attentional control.* Radboud University Nijmegen, Nijmegen, The Netherlands.
99. Azar, M.G. (2012). *On the theory of reinforcement learning: Methods, convergence analysis and sample complexity.* Radboud University Nijmegen, Nijmegen, The Netherlands.
100. Meeuwissen, E.B. (2012). *Cortical oscillatory activity during memory formation.* Radboud University Nijmegen, Nijmegen, The Netherlands.
101. Arnold, J.F. (2012). *When mood meets memory: Neural and behavioral perspectives on emotional memory in health and depression.* Radboud University Nijmegen, Nijmegen, The Netherlands.

102. Gons, R.A.R. (2012). *Vascular risk factors in cerebral small vessel disease: A diffusion tensor imaging study.* Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
103. Wingbermühle, E. (2012). *Cognition and emotion in adults with Noonan syndrome: A neuropsychological perspective.* Radboud University Nijmegen, Nijmegen, The Netherlands.
104. Walentowska, W. (2012). *Facing emotional faces. The nature of automaticity of facial emotion processing studied with ERPs.* Radboud University Nijmegen, Nijmegen, The Netherlands.
105. Hoogman, M. (2012). *Imaging the effects of ADHD risk genes.* Radboud University Nijmegen, Nijmegen, The Netherlands.
106. Tramper, J. J. (2012). *Feedforward and feedback mechanisms in sensory motor control*. Radboud University Nijmegen, Nijmegen, The Netherlands.
107. Van Eijndhoven, P. (2012). *State and trait characteristics of early course major depressive disorder.* Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
108. Visser, E. (2012). *Leaves and forests: Low level sound processing and methods for the large-scale analysis of white matter structure in autism*. Radboud University Nijmegen, Nijmegen, The Netherlands.
109. Van Tooren-Hoogenboom, N. (2012). *Neuronal communication in the synchronized brain. Investigating the functional role of visually-induced gamma band activity: Lessons from MEG.* Radboud University Nijmegen, Nijmegen, The Netherlands.
110. Henckens, M.J.A.G. (2012). *Imaging the stressed brain. Elucidating the time- and region-specific effects of stress hormones on brain function: A translational approach.* Radboud University Nijmegen, Nijmegen, The Netherlands.
111. Van Kesteren, M.T.R. (2012). *Schemas in the brain: Influences of prior knowledge on learning, memory, and education.* Radboud University Nijmegen, Nijmegen, The Netherlands.
112. Brenders, P. (2012). *Cross-language interactions in beginning second language learners.* Radboud University Nijmegen, Nijmegen, The Netherlands.
113. Ter Horst, A.C. (2012). *Modulating motor imagery. Contextual, spatial and kinaesthetic influences.* Radboud University Nijmegen, Nijmegen, The Netherlands.
114. Tesink, C.M.J.Y. (2013). *Neurobiological insights into language comprehension in autism: Context matters*. Radboud University Nijmegen, Nijmegen, The Netherlands.
115. Böckler, A. (2013). *Looking at the world together. How others' attentional relations to jointly attended scenes shape cognitive processing.* Radboud University Nijmegen, Nijmegen, The Netherlands.
116. Van Dongen, E.V. (2013). *Sleeping to Remember. On the neural and behavioral mechanisms of sleep-dependent memory consolidation.* Radboud University Nijmegen, Nijmegen, The Netherlands.
117. Volman, I. (2013). *The neural and endocrine regulation of emotional actions.* Radboud University Nijmegen, Nijmegen, The Netherlands.
118. Buchholz, V. (2013). *Oscillatory activity in tactile remapping.* Radboud University Nijmegen, Nijmegen, The Netherlands.
119. Van Deurzen, P.A.M. (2013). *Information processing and depressive symptoms in healthy adolescents*. Radboud University Nijmegen, Nijmegen, The Netherlands.
120. Whitmarsh, S. (2013). *Nonreactivity and metacognition in mindfulness.* Radboud University Nijmegen, Nijmegen, The Netherlands.
121. Vesper, C. (2013). *Acting together: Mechanisms of intentional coordination.* Radboud University Nijmegen, Nijmegen, The Netherlands.
122. Lagro, J. (2013). *Cardiovascular and cerebrovascular physiological measurements in clinical practice and prognostics in geriatric patients*. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
123. Eskenazi, T.T. (2013). *You, us & them: From motor simulation to ascribed shared intentionality in social perception.* Radboud University Nijmegen, Nijmegen, The Netherlands.
124. Ondobaka, S. (2013). *On the conceptual and perceptual processing of own and others' behavior.* Radboud University Nijmegen, Nijmegen, The Netherlands.
125. Overvelde, J.A.A.M. (2013). *Which practice makes perfect? Experimental studies on the acquisition of movement sequences to identify the best learning condition in good and poor writers.* Radboud University Nijmegen, Nijmegen, The Netherlands.

126. Kalisvaart, J.P. (2013). *Visual ambiguity in perception and action*. Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.
127. Kroes, M. (2013). *Altering memories for emotional experiences*. Radboud University Nijmegen, Nijmegen, The Netherlands.
128. Duijnhouwer, J. (2013). *Studies on the rotation problem in self-motion perception*. Radboud University Nijmegen, Nijmegen, The Netherlands.
129. Nijhuis, E.H.J (2013). *Macroscopic networks in the human brain: Mapping connectivity in healthy and damaged brains*. University of Twente, Enschede, The Netherlands
130. Braakman, M. H. (2013). *Posttraumatic stress disorder with secondary psychotic features. A diagnostic validity study among refugees in the Netherlands*. Radboud University Nijmegen, Nijmegen, The Netherlands.
131. Zedlitz, A.M.E.E. (2013). *Brittle brain power. Post-stroke fatigue, explorations into assessment and treatment.* Radboud University Nijmegen, Nijmegen, The Netherlands.
132. Schoon, Y. (2013). *From a gait and falls clinic visit towards self-management of falls in frail elderly.* Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.
133. Jansen, D. (2013). *The role of nutrition in Alzheimer's disease - A study in transgenic mouse models for Alzheimer's disease and vascular disorders.* Radboud University Nijmegen, Nijmegen, The Netherlands.
134. Kos, M. (2013). *On the waves of language - Electrophysiological reflections on semantic and syntactic processing*. Radboud University Nijmegen, Nijmegen, The Netherlands.
135. Severens, M. (2013). *Towards clinical BCI applications: Assistive technology and gait rehabilitation*. Radboud University Nijmegen, Nijmegen, Sint Maartenskliniek, Nijmegen, The Netherlands.
136. Bergmann, H. (2014). *Two is not always better than one: On the functional and neural (in)dependence of working memory and long-term memory.* Radboud University Nijmegen, Nijmegen, The Netherlands.
137. Wronka, E. (2013). *Searching for the biological basis of human mental abilitites. The relationship between attention and intelligence studied with P3.* Radboud University Nijmegen, Nijmegen, The Netherlands.
138. Lüttjohann, A.K. (2013). *The role of the cortico-thalamo-cortical system in absence epilepsy.* Radboud University Nijmegen, Nijmegen, The Netherlands.
139. Brazil, I.A. (2013). *Change doesn't come easy: Dynamics of adaptive behavior in psychopathy.* Radboud University Nijmegen, Nijmegen, The Netherlands.
140. Zerbi, V. (2013). *Impact of nutrition on brain structure and function. A magnetic resonance imaging approach in Alzheimer mouse models.* Radboud University Nijmegen, Nijmegen, The Netherlands.
141. Delnooz, C.C.S. (2014). *Unravelling primary focal dystonia. A treatment update and new pathophysiological insights.* Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.
142. Bultena, S.S. (2013). *Bilingual processing of cognates and language switches in sentence context*. Radboud University Nijmegen, Nijmegen, The Netherlands.
143. Janssen, G. (2014). *Diagnostic assessment of psychiatric patients: A contextual perspective on executive functioning.* Radboud University Nijmegen, Nijmegen, The Netherlands.
144. Piai, V. Magalhães (2014). *Choosing our words: Lexical competition and the involvement of attention in spoken word production*. Radboud University Nijmegen, Nijmegen, The Netherlands.
145. Van Ede, F. (2014). *Preparing for perception. On the attentional modulation, perceptual relevance and physiology of oscillatory neural activity.* Radboud University Nijmegen, Nijmegen, The Netherlands.
146. Brandmeyer, A. (2014). *Auditory perceptual learning via decoded EEG neurofeedback: a novel paradigm.* Radboud University Nijmegen, Nijmegen, The Netherlands.
147. Radke, S. (2014). *Acting social: Neuroendocrine and clinical modulations of approach and decision behavior.* Radboud University Nijmegen, Nijmegen, The Netherlands.
148. Simanova, I. (2014). *In search of conceptual representations in the brain: towards mind-reading.* Radboud University Nijmegen, Nijmegen, The Netherlands.
149. Kok, P. (2014). *On the role of expectation in visual perception: A top-down view of early visual cortex*. Radboud University Nijmegen, Nijmegen, The Netherlands.
150. Van Geldorp, B. (2014). *The long and the short of memory: Neuropsychological studies on the interaction of working memory and long-term memory formation.* Radboud University Nijmegen, Nijmegen, The Netherlands.

ISBN 978-94-91027-86-4

Donders Institute
for Brain, Cognition and Behaviour

Radboud University Nijmegen