# Neurocognitive mechanisms of visual working memory and episodic memory in healthy aging and after stroke

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## Selma Lugtmeijer

# Neurocognitive mechanisms
# of visual working memory
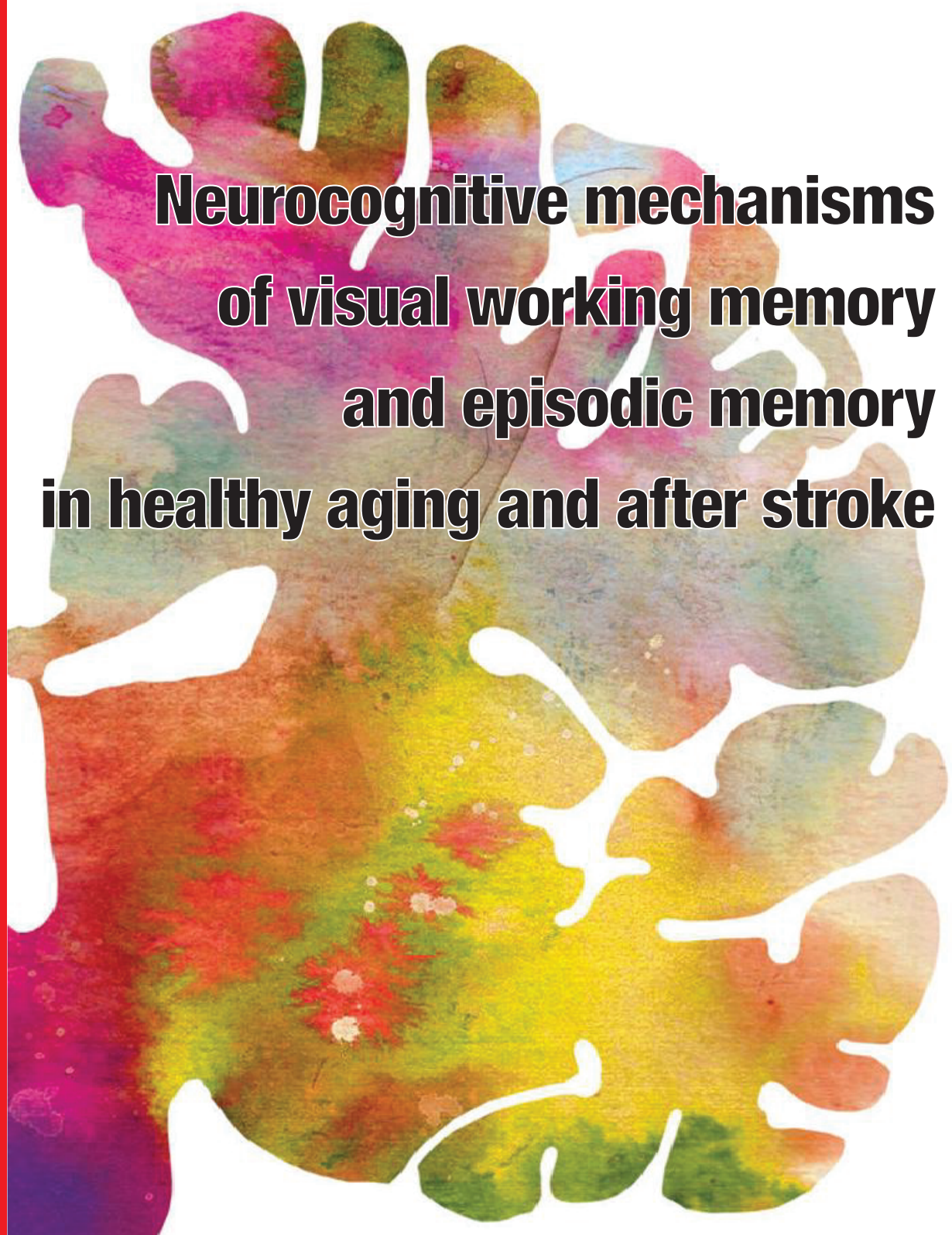# and episodic memory
# in healthy aging and after stroke

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ACADEMISCH PROEFSCHRIFT

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aan de Universiteit van Amsterdam
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## Contents

"When I name forgetfulness, and know, too, what I name,
whence should I know it if I did not remember it?
I do not say the sound of the name, but the thing which it signifies which,
had I forgotten, I could not know what that sound signified.
When, therefore, I remember memory, then is memory present with itself,
through itself. But when I remember forgetfulness,
there are present both memory and forgetfulness, memory,
whereby I remember, forgetfulness, which I remember.
But what is forgetfulness but the privation of memory?"

*Saint Augustine (354-430)*

Confessions
Translated by J. G. Pilkington
Book X Chapter 16
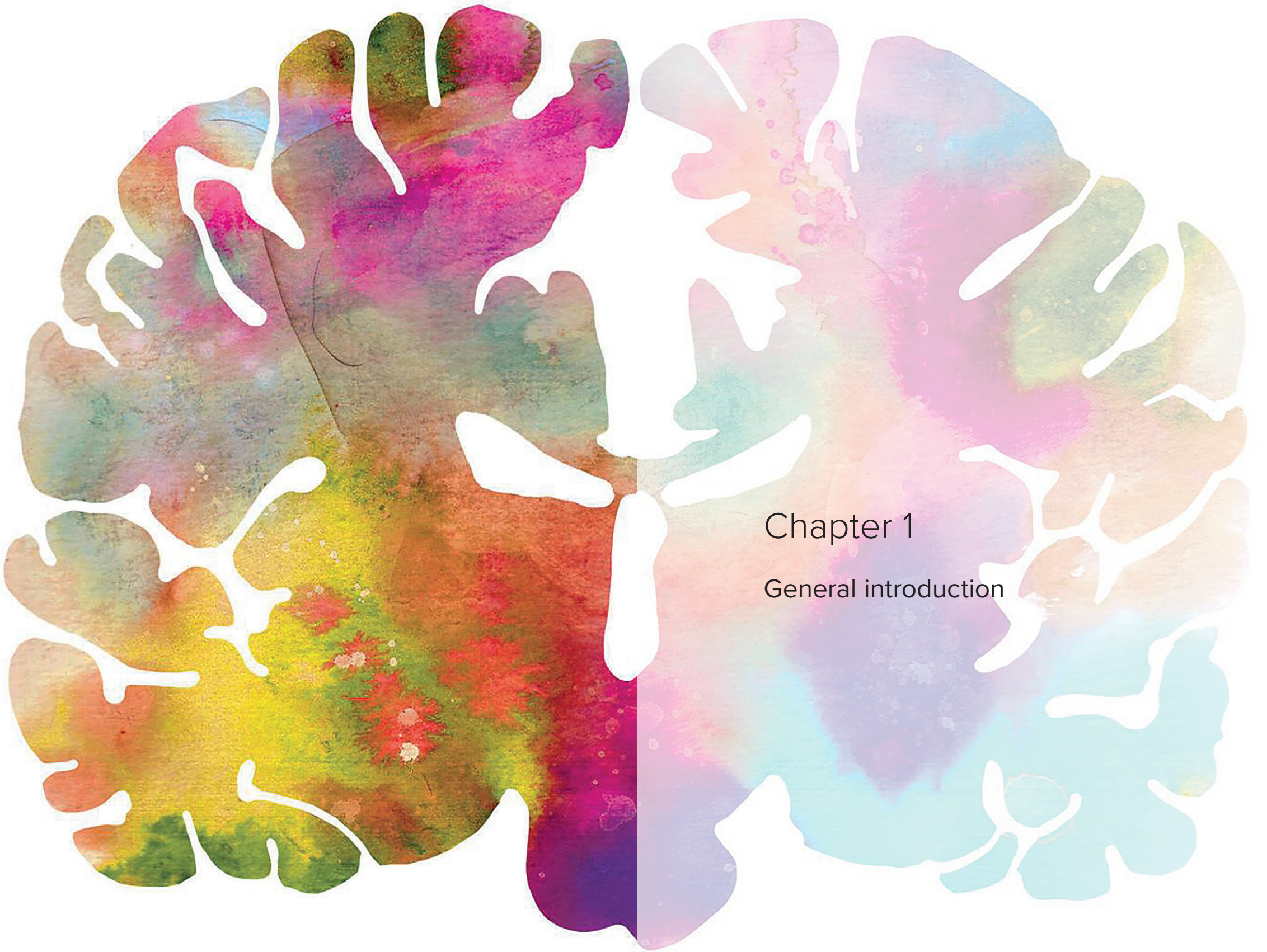
Chapter 1

General introduction

When you look at your surroundings, you see scenes and objects that have a multitude of visual features: shape, color, texture, size, orientation, and location. The moment you look away or close your eyes, you can remember which object was where and what features belong to it. You are able to form an internal representation of features and their conjunctions – such as yellow, purple and orange colored spherical lanterns that hang over the street, a rectangular white van and a brown tuktuk in the distance, and person with a black shirt (all are on the picture on the previous page). Some representations only last for a brief period – you had probably forgotten most of it – while other representations remain over a longer period of time – I remember details of the picture because it was taken during one of my holidays.

In the example above, memory for visual information is needed, for separate features and their interrelations. Our ability to remember visual information is impressive and essential to most of our daily tasks. People can recognize objects that they have seen only briefly or long ago, from different angles, and in different lighting conditions. To understand memory, it is essential to focus both on systems or prosses and the nature of representations therein. Visual memory has been studied less extensively than verbal memory and the neural mechanisms are not fully understood. The aim of this thesis is to contribute to the understanding of visual memory based on insights from studying healthy elderly and stroke patients.

## Multiple memory systems

Case studies in the second half of the twentieth century led to the suggestion of a neuropsychological double dissociation between sort-lived memory representations and permanently stored memories. (Scoville & Milner, 1957) reported the famous case study of patient H.M. who after a bilateral medial temporal lobe resection, was virtually unable to form new memories, while his performance on memory tests with short retention delays was intact. A contrasting case study is that of patient K.F., who had damage to the left inferior parietal lobe and who showed a greatly reduced short-term memory capacity yet performed normal on long-term memory tests (Shallice & Warrington, 1970). Following these initial findings more patients were identified with similar patterns of impaired and spared abilities in memory subprocesses. This resulted in the idea of independent functioning of short-term and long-term memory systems based on different brain structures (Warrington, Logue, & Pratt, 1971). An early influential model is the multi-store model by (Atkinson & Shiffrin, 1968) that distinguishes between the sensory registers where sensory information resides for a brief moment, the

short-term store where a limited amount of information is held as long as it is rehearsed, and the fairly permanent long-term store.

## Working memory

In the 1950s and 1960s, short-term memory was thought of as a rapidly decaying system that could hold 7 +/-2 items. Studies focused on measuring short-term memory capacity in terms of number of items, and estimates of the number was moderated to about four items (Cowan, 2008; Moscovitch, 2012). The notion that short-term memory is not merely a passive storage of information but also allows manipulation of information led to the development of a multicomponent system for working memory (Baddeley & Hitch, 1974; Baddeley, 2000), Fig 1.). Early experimental and theoretical work was based almost exclusively on verbal memory both in the model of Atkinson and Shiffrin (1968) and Baddeley and Hitch (1974). The multicomponent model describe two passive stores for different materials (though the visuo-spatial system was only briefly mentioned), a central executive processes for mental operations, and a later added episodic temporary store for multimodal integration (Baddeley, 2000). The limited capacities of the phonological loop and the visuospatial sketchpad are typically measured by tasks that require passive maintenance of verbal and visuo-spatial information respectively (often referred to as short-term memory). Frequently used tasks to assess short-term memory capacity are forward span tasks. The functioning of the central executive, which can be described as the attentional control system, is measured by working memory tasks that involve not only passive maintenance but also active processing, resulting in increased task demands. Tasks might require resorting of items, as in backward span or sorting span tasks, or updating of information, as in for example N-back tasks in which the current item needs to be compared in mind to N items previously. The episodic buffer was added to the model to account for some problems that could not be solved by the initial three-component model. This multidimensional system integrates information from multiple sources including long-term memory and perception. Importantly, the episodic buffer allows for binding information in working memory, such as complex representations from separate sensory sources as location, smell and tactile features of objects (Baddeley, 2000, 2012).

Different components of the model are measured by different tasks and as working memory encompasses multiple processes, it has been associated with a broad range of brain regions, depending on specific task requirements. As a logical consequence divergent result have been reported on neural correlates for working
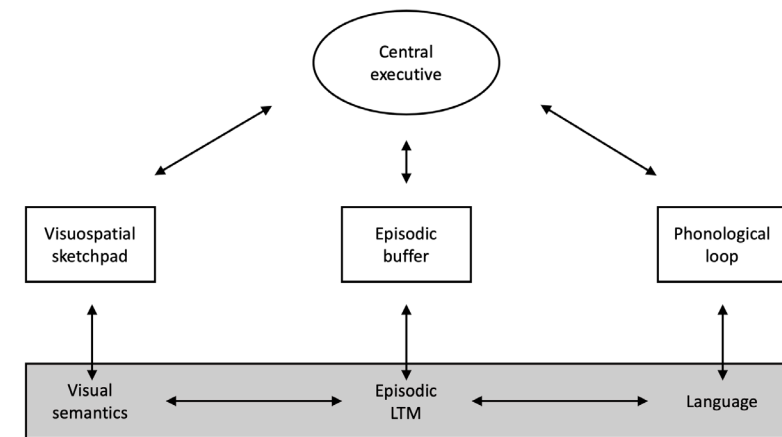


**Fig. 1.** Extended model of working memory in white. The shaded area indicates the link between long-term knowledge and working memory. Adapted from Baddeley (2000).

memory. Working memory representations are found across sensory, parietal, temporal, and prefrontal cortices (Christophel, Klink, Spitzer, Roelfsema, & Haynes, 2017). Representations in different regions might vary in different levels of abstraction, from sensory representations in primary sensory areas to abstract representations frontal areas (Christophel et al., 2017), regions might depend and be based on complexity of stimuli (Bancroft, Hockley, & Servos, 2014). Typically reported in neuroimaging and electrophysiology studies, is activation of a wide- spread front-oparietal network during working memory tasks. A task independent "core" network for working memory has been identified in a meta-analysis of fMRI experiments which encompassed bilateral supplementary motor area, inferior frontal gyrus, anterior insula and the intraparietal sulcus/cortex (Rottschy et al., 2012).

## Long-term memory

Long-term memory refers to a vast store of fairly permanent knowledge and a selection of prior events that is not currently active (Cowan, 2008). Widely used is the classification of long-term memory into subsystems as defined by (Squire, 1992; Fig. 2.). At the first level it distinguishes between declarative and non-declarative memory. Conscious recollection of events and facts relies on declarative memory. This is the type of memory that is commonly referred to in everyday situations.

In contrast, non-declarative memory encompasses forms of non-conscious memory abilities, amongst which skill-based (or procedural) learning. In this thesis I will focus on episodic memory, defined as conscious experiences in space and time (Tulving, 1993). More specifically, on recognition and forgetting of previously presented study materials.
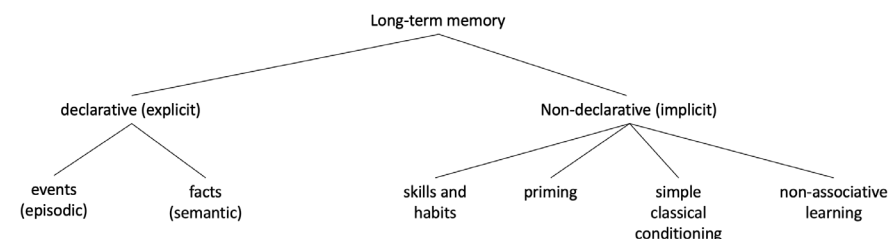


**Fig. 2.** Classification of long-term memory. Adapted from (Squire, 1992).

Even though long-term memory is referred to as unlimited and permanent, everyone experiences forgetting in daily life. Forgetfulness is a common complaint in normal aging and in various forms of brain disease. People with Alzheimer's dementia or mild cognitive impairment have a deficit in the formation of episodic memory, while patients with temporal lobe epilepsy show a pattern of accelerated forgetting after a long delay despite normal acquisition and recall over short delays. In stroke patients or patients with traumatic brain injury, memory impairments are heterogeneous, depending on lesion characteristics.

Neural correlates for episodic memory bring us back to the patient H.M. with bilateral medial temporal lobe resection. A vast amount of patient and later non-invasive studies have followed up on this initial finding, studying the role of the hippocampus and surrounding medial temporal lobe in memory. A meta-analysis (Spaniol et al., 2009) on brain activations during episodic memory processes showed the involvement of the medial temporal, prefrontal and parietal regions, more pronounced in the left hemisphere. More specifically, anterior hippocampus showed stronger activation during episodic encoding, while more posterior medial temporal lobe regions showed more involvement in retrieval, possibly associated with contextual binding. In the frontal cortex, the left dorsolateral and ventrolateral prefrontal cortex were associated with encoding success. The intra-parietal sulcus and superior parietal lobe showed retrieval-related activation.

## The relation between working memory and episodic memory

Multi-store models of memory, like the model by Baddeley and Hitch (1974; Baddeley, 2000), assume separate temporary and permanent (long-term) storage systems. Evidence is based on case studies of patients with brain damage, as those described above, that demonstrate impairment in one memory system with the other being relatively intact. Additional evidence comes from behavioral studies on verbal memory showing phonological confusions at short retention intervals, and semantic confusions at longer intervals, and problems that arise in serial order tasks (reviewed in Norris, 2017).

Not all memory models that distinguish between different processes for short-term and long-term memory necessarily imply different neural mechanisms. Atkinson and Shiffrin wrote in 1971 (p. 4): "Our account of short-term and long-term storage does not require that the two stores necessarily be in different parts of the brain or involve different physiological structures. One might consider the short-term store simply as being a temporary activation of some portion of the long-term store." An influential unitary model of memory is the "embedded-processes model" by Cowan (1988, 2017, 2019; Fig. 3). According to this model, working memory is nothing more than memory representations that are in a temporarily activated state, so they are easily accessible. There are three hierarchically arranged faculties, 1) long-term memory, 2) a subset of long-term memory in an activated state, 3) a highly limited subset that is in the focus of
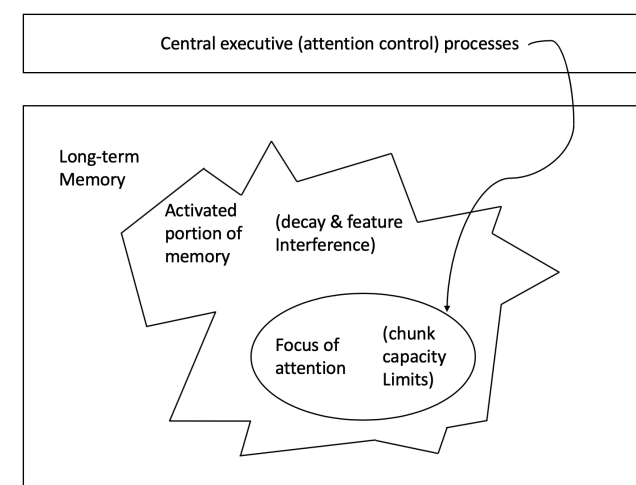


**Fig. 3.** The embedded-processes model with three hierarchically arranged faculties. Adapted from Cowan, 2008.

attention, there is evidence for a single-item focus and for a multi-item focus of attention for 3 or 4 items. In this view, working memory is based on rapid new learning, in which new associations can be formed as new long-term memory traces (Cowan, 2019).

The key distinction between the multi-store models of memory and the activated long-term memory view, is the need for a separate temporary memory store. In order to keep in memory sequences of digits, or different features that belong to an object, simply activating preexisting long-term memory representations does not suffice. In the embedded-processes model, new, rapidly formed memory traces solve the problem of representations that cannot rely only on pre-learned long-term memory. Whether this a satisfactory explanation for working memory functioning is an ongoing debate (Baddeley, Hitch, & Allen, 2019; Cowan, 2019; D'Esposito & Postle, 2015; Norris, 2019; Oberauer, 2009; Shallice & Papagno, 2019).

Pathological cases with specific memory impairments are not immune to critique (Cowan, 2019; Morey, Rhodes, & Cowan, 2019). Cowan (2019) argues that selective impairments in short-term memory with intact long-term memory can be explained by impairment in control processes that are different for short-term and long-term memory and different study materials and retrieval cues, rather than separate stores. An example in this argument is that for short term recall often digits are used, while for episodic memory words are used that provide more possibilities for richer encoding. Neuroimaging studies so far do not provide exclusive evidence either. Observed activations in the same brain regions during working memory and episodic memory tasks does not necessarily imply a single system. Dorsolateral prefrontal regions and the posterior parietal lobe show activation during both working memory and episodic memory. This might reflect common processes like monitoring or phonological processing (Cabeza, Dolcos, Graham, & Nyberg, 2002). Medial temporal lobe activation implicated in working memory might be explained by incidental long-term memory processing during a working memory task (e.g. Bergmann et al., 2015). It is important to keep in mind the correlational nature of neuroimaging; activation does not imply necessity (Catani & Stuss, 2012).

There is an additional challenge in assessing and comparing working memory and episodic memory functions. Working memory is a multifaceted system that comprises processes like encoding, maintenance, updating, temporal ordering, binding, attention, and inhibition. Therefore, it is unsurprising that different working memory tasks tap only partly overlapping components of working memory resulting in a weak correlation between tasks (Redick & Lindsey, 2013). As is the case with working memory, episodic memory consists of different subprocesses, and different tasks tap a variation in encoding, and retrieval conditions. Furthermore, working memory and episodic memory tasks use different stimuli, all with their own specific characteristics (e.g., in terms of verbalizability and perceptual complexity). Such task specific properties may modify the (presumed) relationships between the two memory systems, and stimulus-specific variability across studies makes comparison of working memory and episodic memory performance difficult. Therefore, new task designs are needed in which visual working memory and episodic memory are measured in a way that minimizes task differences.

## Binding in visual working memory and episodic memory

Binding is essential in visual perception, working memory and episodic memory. Perceptual representations depend on a mechanism that binds features belonging to an object (Treisman, 1996). Information from distinct neural populations in the brain (sensitive to color or orientation for example) must be integrated in a way so that people can effortless perceive their complex surroundings. In the multi-component system of working memory, the role of the episodic buffer is to integrate information from different sources, this includes perception, long-term memory, but also imagination (Baddeley, 2000, 2012). In episodic memory, binding is inherent to the definition: conscious experiences in *space and time* (Tulving, 1993).

Recently, it has been suggested that space and time may also have a crucial role in working memory (Schneegans & Bays, 2019). The binding of events or items to temporal and spatial information is considered as extrinsic intra-item binding, or more generally, context binding. Other forms of binding are intrinsic intra-item binding (the binding of features within objects, e.g. color-object), and inter-item binding (e.g. object-object). When discussing binding in this thesis, I refer to extrinsic intra-item binding/context binding. In working memory, space and time are suggested to have a special role in the binding of multiple features. Features like color and orientation that belong to the same object are bound via their shared location. Location of items is encoded automatically, inherent in the structure of retinotopic maps. Evidence for this comes from brain imaging studies show that location can be decoded from imaging data even when location is task-irrelevant. Secondly, studies that show that presenting items sequentially at the same location impairs performance due to interference. Despite reduced performance, people are still able to memorize feature bindings of sequentially presented items. This indicates that temporal conjunctions can also be used to bind features (reviewed in Schneegans & Bays, 2019). For instance, in episodic memory, shared contextual information interferes with recollection (Yonelinas, Ranganath, Ekstrom, & Wiltgen, 2019). You can imagen the situation in which you

go to a park that you know well on Monday and see friend walking, then on Tuesday you go to the same park and you run into a colleague who is working out. A week later can you probably recall both events, but you might mix up who you saw on which day or who was doing what.

## Memory and aging

Situations like the above-mentioned example might be particularly familiar to elderly people. An age-related deficit in associative episodic memory is well established and applies to inter-item binding, as well as to all forms of context binding (Old & Naveh-Benjamin, 2008). This is referred to as the "associative deficit hypothesis" that states that older adults exhibit a disproportionate decrement in memory for bound information, relative to memory for the separate components (e.g. Naveh-Benjamin, 2000; Naveh-Benjamin & Mayr, 2018). An open question is whether binding in working memory is affected to the same extent. Whereas age-related binding deficits are a robust finding in studies of episodic memory, the view on binding deficits in working memory has shifted over the last decade. While some early work suggested that binding in working memory is selectively impaired in healthy aging (Cowan, Naveh-Benjamin, Kilb, & Saults, 2006; Mitchell, Johnson, Raye, Mather, & D'Esposito, 2000), several more recent studies have consistently concluded that there is a general decline of working memory performance in older adults, but no specific impairment for feature binding (Brockmole, Parra, Della Sala, & Logie, 2008; Pertzov, Heider, Liang, & Husain, 2015; Rhodes, Parra, & Logie, 2016).

A second theory of age-related differences in memory performance is the "irrelevant information deficit hypothesis" according to which older adults have more difficulty in inhibiting irrelevant information and removing outdated information from the focus of attention, resulting in inefficient encoding and impaired performance (Campbell & Hasher, 2018; Healey, Campbell, & Hasher, 2008). While hyper-binding of irrelevant information might hamper both working memory and episodic memory performance in older adults, some studies found that in situations where previously irrelevant information becomes relevant, older adults outperform younger adults (Healey et al., 2008). Hyper-binding has mainly been studied in paradigms in which, during a working memory task, relevant and irrelevant was presented simultaneously, followed by a subsequent memory task in which the previous irrelevant information becomes relevant. Older adults perform worse on the working memory task but better on the subsequent memory task compared to young adults (Campbell, Hasher, & Thomas, 2010).

## Memory and brain dysfunction: Lesion-behavior mapping

A different way of studying changes in memory is investigating the consequences of brain damage on different memory functions. Inferring the function of specific brain areas by examining the relationship between brain lesions and subsequent cognitive impairments has a long history. Even though brain-function relationships can now be studied with noninvasive methods measuring activity in the healthy brain, lesion studies identify areas that are *necessary* for a given cognitive function, rather than merely involved (Karnath, Sperber, & Rorden, 2018). Therefore, lesion analyses in patient populations with impaired behavior are a valuable source of knowledge regarding the relation between function and anatomy in the healthy brain. These investigations are complementary to functional MRI studies. Lesion analyses have developed from examining the location of brain damage after a patient had died, to locating a lesion using a CT scan, to mass-univariate and multivariate voxel-based lesion symptom mapping and advanced network analyses in groups of patients. The wide range of possibilities in this field is outside the scope of my thesis. I focused here on voxel-based and atlas-based lesion-symptom mapping. This analysis compares for every area whether it makes a difference for performance if that area is damaged or not by comparing patients with different lesions. One advantage of studying stroke patients is that due to the sudden nature of the brain damage there is a clear association between functional impairment of the brain and behavioral consequences. This is especially true in the acute stage, before functional reorganization. In the chronic phase of stroke lesion analyses are a useful tool to examine neural correlates of chronic deficits (De Haan & Karnath, 2018). Memory deficits are common after stroke with estimates between 11% and 55% (Snaphaan & De Leeuw, 2007). This makes stroke an ideal etiology to study neural correlates of memory.

## Aim and outline of this thesis

In this thesis I focused on the question: "are visual working memory and episodic memory distinct processes with different neural substrates?" Subsequently, I zoomed in on working memory processes and forgetting in long-term memory. The aim was to investigate how subsystems of memory relate at the behavioral and neural level. The focus is on visual memory as models have predominantly been formed based on experiments using verbal materials. To address this, I studied healthy older adults and stroke patients, making use of novel designs based on visual stimuli. I have conducted five studies described in the following chapters.

Working memory and episodic memory decline with age. However, as these systems are typically studied separately, it is largely unknown whether these functions decline following the same course. In **chapter 2**, I studied age-associated differences for visual working memory and episodic memory with a novel task design, developed to measure both processes using the same stimuli. Younger and older adults performed an object 2-back working memory task followed by a surprise subsequent recognition memory task that assessed incidental encoding of the stimuli from the 2-back task. By using the same stimuli and addressing working memory and episodic memory in one task design, working memory and episodic memory performance could be compared directly in both age groups.

Following up on chapter 2, **Chapter 3** describes a study in which the same task design was used to compare visual working memory and episodic memory in stroke patients and a stroke-free control group. My main goal was to investigate whether stroke patients can provide evidence for the (lack of) independence of working memory and episodic memory; the central question in the debate on multi-store models versus unitary models of memory. Studying post-stroke memory impairments and lesion-behavior relations allows for the study of causal relations whereas imaging studies in healthy participants only show correlations between brain activation and behavior.

While chapter 2 and 3 focused on the relationship between visual working memory and episodic memory, the next chapters are concerned with the study of each of these processes. First, I looked at visual working memory. This is required for many everyday tasks and important for the formation of subsequent episodic memory. In **chapter 4**, I examined whether stroke can result in specific impairments of feature binding in visual working memory. I combined computational modeling and structural MRI to investigate feature binding for colors and locations. Stroke patients and age-matched controls were assessed in a delayed-reproduction task. Participants viewed a sample array of colored disks, and after a brief delay either had to report the color of one disk cued by its location or the location of one disk cued by its color on a continuous scale. Model parameters were used to estimate reporting or binding deficits and lesion-symptom mapping to identify lesion locations associated with deficits.

Performance on the delayed-reproduction task used in chapter 4, relies according to the multicomponent model of working memory on the visuospatial sketchpad. How different components of this model are affected by stroke is investigated in a meta-analysis and systematic review in **chapter 5**. A coherent overview of post-stroke working memory deficits is lacking. From a clinical perspective post-stroke working memory dysfunction is relevant for it has been found to be the only cognitive function predictive for poor functional outcome in long term follow-up. As patient studies often have small samples and most studies only include some aspects of the multicomponent system of working memory, quantitatively reviewing all available studies on this topic will help to provide a more comprehensive picture of deficits in working memory after stroke.

A second clinically relevant question is how much people forget after initial learning. Classic hippocampal amnesia is characterized by rapid forgetting (i.e., decay of memory which is already present after a 20-30 minute delay, which for instance is observed in Alzheimer's dementia), while the concept of accelerated long-term forgetting (ALF) refers to abnormal forgetting over long delays (days to weeks) despite normal acquisition. The behavioral study in **chapter 6** describes forgetting in episodic memory over different delays in stroke patients and stroke-free controls. A direct recognition task was followed by a delayed recognition task over a time span frequently used in clinical assessment (20 minutes). A second delayed test followed one week later. Forgetting rates over a short retention interval and over a long retention interval can give insight in different profiles of forgetting and might be used to identify patients with ALF that are missed in standard clinical practice.

Finally, **chapter 7** summarizes the results of the chapters in this thesis, followed by a discussion on how our results contribute to theoretical models of memory. In addition, methodological considerations, clinical relevance of this work, and future perspectives are discussed.

# Chapter 2

## Visual working memory and episodic memory in younger and older adults

## Abstract

Previous studies showed that both working memory and episodic memory decline with age. However, as working memory and episodic memory are typically studied separately, it is largely unknown whether age-associated differences are similar for working memory and episodic memory and how they relate. A task design was developed in which visual working memory and episodic memory performances were measured using the same stimuli, with both tasks involving context binding. A 2-back working memory task was followed by a surprise subsequent recognition memory task that assessed incidental encoding of object locations of the 2-back task. The study compared performance of younger (N=30; $M$age=23.5, $SD$age=2.9, range 20-29) and older adults (N=29; $M$age=72.1, $SD$age=6.8, range 62-90). Older adults performed worse than younger adults on both tasks. There was no interaction between task and age-group. In younger, but not in older adults, performance on the two tasks was related. Furthermore, the number of errors on lure trials was the same in both age groups. We conclude that although age differences (Young > Older) are similar in the visual working memory and incidental associative memory tasks, the relationship between the two memory systems differs as a function of age group. Longitudinal research is needed to investigate life-span changes in the relationship between working and episodic memory. As some neurodegenerative diseases are characterized by specific types of memory impairment, it is important to have a profile of functioning of memory subsystems for unimpaired older adults.

## Introduction

A decline in memory function is a common complaint of older adults. However, memory function is not a unitary construct, but consists of multiple memory systems that may be differentially affected by aging (Tulving, 1983; see Craik & Rose, 2012 for a review). For instance, procedural memory and semantic memory are relatively spared whereas substantial decline has been demonstrated in working memory and episodic memory (Craik & Rose, 2012). To date, there is debate on how these systems are related how that is affected by aging.

Several theories of memory and aging have been proposed (for a recent review, see Park & Festini, 2017). Two theoretical frameworks are of particular interest here, as they specifically address working memory and episodic memory. The first is the "associative deficit hypothesis" that states that older adults exhibit a disproportionate decrement in memory for bound, associative information, relative to memory for the associated items, and this is due to problems both with binding and retrieval (e.g. Chalfonte & Johnson, 1996; Naveh-Benjamin, 2000). An example of associative memory is context memory, which involves the binding of features to objects, such as spatial and temporal properties. Context information aids the retrieval of memories and has been found to be more impaired than item memory in older adults compared to younger adults (e.g. Chalfonte & Johnson, 1996; Kessels, Hobbel, & Postma, 2007; Naved-Benjamin, 2000; Naveh-Benjamin, Guez, Kilb, & Reedy, 2004; Naveh-Benjamin, Hussain, Guez, & Bar-On, 2003; see meta-analyses by Spencer & Raz, 1995). Whereas age-related binding deficits are a robust finding in studies of long-term memory, research during the last decade has demonstrated that both item-context binding and item-item binding in working memory may be additionally affected in older adults (e.g. Chen & Naveh-Benjamin, 2012; Cowan, Naveh-Benjamin, Kilb, & Saults, 2006; Fandakova, Sander, Werkle-Bergner, & Shing, 2014; Peterson & Naveh-Benjamin, 2016; but see Read, Rogers, & Wilson, 2016) while within-item binding seems to be relatively spared by age (e.g. Parra, Abrahams, Logie, & Della Sala, 2009).

A second theory that might explain age-related differences in memory performance is the "irrelevant information deficit hypothesis" according to which older adults have relatively more difficulty in inhibiting irrelevant information and updating in the presence of distraction, resulting in inefficient encoding and impaired performance (for a review, see Healey, Campbell, & Hasher, 2008; Hasher & Zacks, 1988). While irrelevant information might hamper both working memory and episodic memory performance in older adults, some studies found that in situations where previously irrelevant information becomes relevant older adults outperform younger adults (Healey et al., 2008). Studies discussed in the review by Healey et al. (2008) show that older adults can benefit more than

younger adults from previously irrelevant verbal distractors in subsequent tasks, like a word fragment completion task or RAT problems. Campbell, Hasher, and Thomas (2010) investigated associations between words and objects and reported hyper-binding in older adults, which means that older adults encode irrelevant co-occurrences and are able to use this in a subsequent task. Younger and older adults performed a 1-back task with line drawings of objects with irrelevant words superimposed. After a 10-minute delay 16 object-word pairs were presented in a study phase, half of the pairs were intact pairs from the 1-back task, the other half disrupted pairs. The study phase was directly followed by a testing phase in which the objects were shown and participants had to recall the corresponding words. Critical was the age-by-pair-type interaction with no differences between preserved and disrupted pairs in younger adults and an advantage for preserved pairs in older adults, showing that older adults, unlike younger adults, were able to use the associations incidentally learned during the 1-back task.

Inconclusive results from previous studies concerning effects of aging on memory may be due to task differences. Working memory is a multifaceted system that comprises processes like encoding, maintenance, updating, temporal ordering, binding, attention and inhibition. Therefore, it is unsurprising that different working memory tasks tap only partly overlapping components of working memory resulting in a weak correlation between tasks (Redick & Lindsey, 2013). Furthermore, the degree of age-related decline may also depend on task characteristics. That is, more complex working memory tasks being more sensitive to aging than less complex ones (Bopp & Verhaeghen, 2005). As with working memory, episodic memory consists of different sub-processes, variation in encoding and retrieval conditions influences age-associated differences (review by Tromp, Dufour, Lithfous, Pebayle, & Després, 2015). Furthermore, previous working and episodic memory tasks have often used different stimuli, all with their own specific charac-teristics (e.g., in terms of verbalizability, perceptual complexity and sometimes even auditory versus visual presentation). Such task-specific properties may modify the relationships between the two memory systems, and stimulus-specific variability across studies makes comparison of working memory and episodic memory performance difficult.

A way to reduce task differences and assess the relationship between the subsystems is to use the same stimuli in a within-subjects design. To date, three studies investigated working memory and episodic memory by testing incidental encoding during the working memory task with a subsequent memory task (Bergmann, Rijpkema, Fernández, & Kessels, 2012; Van Geldorp et al., 2015; Werkle-Bergner, Freunberger, Sander, Lindenberger, & Klimesch, 2012). Two studies used a delayed match-to-sample working memory task during which participants needed to keep pairs, each consisting of both a house and a face stimulus, in mind

and make a judgment. In an unexpected subsequent memory task, participants had to choose from two pairs of faces and houses, the pair they had seen before. Van Geldorp et al. (2015) compared the performance of younger and older adults and showed a similar effect of age on both tasks. A limitation of this study was the complexity of the stimuli used, which resulted in near chance-level performance on the subsequent memory task in older adults (Van Geldorp et al., 2015). A second consequence of using complex stimuli is the possibility that long-term memory was recruited during the working memory task due to an overload of working memory capacity (Jeneson & Squire, 2012) resulting in both tasks relying on the same memory subsystem. Bergmann et al. (2012) used the same paradigm in an event-related fMRI design with healthy students showing only partial overlap in the recruitment of brain regions for working and episodic memory. This suggests that the two systems may be differentially susceptible to the effects of age. A third study assessing working memory and episodic memory took relevant versus irrelevant information and age differences into consideration in new-old judgments of scenes (Werkle-Bergner et al., 2012). Each stimulus was preceded by a cue that indicated whether the stimulus needed to be remembered or not. Younger adults showed higher recognition on both tasks. On the subsequent episodic memory task both groups performed at chance level for the stimuli cued as not-to-be remembered indicating successful inhibition of irrelevant information. No comparison was made between working memory and episodic memory performance. Thus, the question how working memory and episodic memory relate and if successful processing in working memory is required for successful long-term memory is still open to debate.

In order to shed some light on this unresolved issue in relation to age differences, we developed a task design to measure both working memory and long-term memory for the same visual stimuli in a within-subjects design taking into account findings and limitations from previous studies. As working memory measure, we used an *N*-back task in which participants have to respond when an item in a sequence of presentations matches the item *N* trials before (Kirchner, 1958). The *N*-back task we designed contained easy-to-name objects to avoid a floor effect on the subsequent memory task and contained no relevant associations apart from temporal order to reduce the chance of recruitment of long-term memory during the working memory task. The *N*-back task measures working memory as defined by Unsworth and Engle (2007), highlighting two essential working-memory components: 1) cognitive control is needed to override automatic responses, 2) the maintenance and retrieval of novel information is required in the presence of distracting information where a discrimination process differentiates between relevant and irrelevant information (see Cowan, 2017, for a review). In the *N*-back task, only the item of the relevant lag needs to be compared to the current

item in a continuous sequence, while control is needed to suppress responses to items of other lags and a discrimination process is needed to decide relevance of maintained items. This design allows for analyzing different types of errors. Errors on lure trials (i.e., trials with an object corresponding to a different but close lag to two) indicates responses based on familiarity rather than successful updating. Finally, the object component made the task suitable to test subsequent memory formation.

The *N*-back task was followed by an unexpected memory task, during which object-location associations incidentally encoded during the working memory task were tested. This subsequent recognition memory task relies on long-term memory, not only because of the longer retention interval, but also because of the large number of items that need to be stored and the associations between object and location that are necessary for successful performance (Jeneson & Squire, 2012). The meta-analysis by Old and Naveh-Benjamin (2008) showed that intentional encoding instructions resulted in a larger age effect compared to incidental encoding instructions. However, we chose incidental encoding to minimize interference of long-term memory encoding during the working memory task, so that both tasks were non-dual tasks (Bergmann et al., 2012). Using the same stimuli and similar context binding in both tasks in a within-subjects design allows us to compare the working memory with the episodic memory performance and assess the relationship. The following research questions were addressed 1) do working memory and episodic memory performance show similar age differences when using the same stimuli? 2) how are working memory performance and episodic memory performance related in younger and older adults? 3) are there age-related differences in response patterns?

To answer the research questions, 30 younger and 30 older adults were tested on the working memory and episodic memory tasks. The results may have repercussions for several different theoretical accounts, but a particular set of hypotheses can be proposed based on the associative deficit hypothesis and the irrelevant information hypothesis. The associative deficit hypothesis predicts similar age-associated differences on the working memory and subsequent memory task as has been shown before in an item-item binding task (Chen & Naveh-Benjamin, 2012). Previous studies have shown that both object-temporal order and object-location binding are similarly sensitive to aging in long-term memory paradigms (Old & Naveh-Benjamin, 2008), furthermore, age-related binding deficits have been reported in working memory for object-location associations (Cowan et al.,2006; Peterson & Naveh-Benjamin, 2016). The correlation between performance on the two tasks is expected to be positive, indicating that both systems are related by a common mechanism. The irrelevant information deficit hypothesis predicts worse performance of older adults on the

working memory task but a possible advantage on the subsequent memory task. Lack of inhibition of irrelevant objects from different lags than two, might impair performance on the *N*-back task, while encoding of irrelevant location information during the working memory task in older adults might result in an advantage on the subsequent memory task. High performers on the *N*-back task are better at inhibition so it can be expected that they are the low performers on the subsequent memory task, therefore a negative correlation is predicted. As aging has a stronger effect on recollection than on familiarity older adults are expected to make more mistakes on lure trials in the working memory task. Correctly identified targets in the working memory task are expected to be processed better than missed targets and therefore more likely to be bound to the correct location in episodic memory in both younger and older adults. A signal-detection approach was used to analyze the data, which has been suggested for evaluating the binding deficit hypothesis (Cowan et al., 2006). Mixed results have been reported in the literature regarding the effects of age on response bias. For instance, a slightly more liberal response bias in older adults was found by Bender, Naveh-Benjamin, and Raz (2010), while others reported more a conservative response bias in older adults (e.g. Cowan et al., 2006; Read et al., 2016).

## Method

### Participants

Thirty older adults and 30 younger adults participated in the study between February and December 2016. Older adults were aged above sixty and younger adults were between twenty and thirty years old (in line with meta-analyses by Bopp & Verhaeghen 2005; Koen & Yonelinas, 2014; Old & Naveh-Benjamin, 2008). Participants from both groups were matched on sex and level of education based on the Dutch educational system (range 1-7, low to highly educated; Verhage, 1964). Exclusion criteria were indication for cognitive impairment based on the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) using a cut-off of 23 (Luis, Keegan, & Mullan, 2009), the diagnosis of a cognitive disorder or a psychiatric history. One older adult (age 69, male, education level 6) was excluded from analyses based on a MoCA score below the cut-off, resulting in a final sample of 29 older adults. Participants were recruited from social networks and received monetary compensation (EUR 10,00) for their participation. Informed consent was obtained from all participants according to the Declaration of Helsinki. The study was approved by the ethics committee of the faculty of social sciences of the Radboud University. Descriptive characteristics and neuropsychological test results are presented in Table 1.

**Table 1** Descriptives, neuropsychological measures and comparisons between two age groups.

|  | Older adults | Younger adults | Statistics | *p*-value |
|---|---|---|---|---|
| Sex (m:f) | 13:16 | 14:16 | $X^2$(1)=.020 | .887 |
| Age (*M, SD,* range) | 72.1 (6.8, 62-90) | 23.5 (2.9, 20-29) | | |
| Education level[c] (*Mdn*, range) | 6 (3-7) | 6 (4-7) | *U*=398.0 *z*=-.600, | .549 |
| MoCA (*M, SD,* range) | 26.9 (1.8, 24-29) | 27.7 (1.6, 24-30) | *t*(57)=-1.92 | .060 |
| NART IQ (*M, SD*) | 114.3 (10.3) | 96.7 (10.5) | *t*(56)[a]=6.42 | <.001 |
| Corsi forward[b] (*M, SD*) | 40.2 (14.4) | 57.9 (20.1) | *t*(57)=-3.88 | <.001 |
| Corsi backward[b] (*M, SD*) | 42.0 (14.7) | 62.6 (17.1) | *t*(57)=-4.96 | <.001 |
| Doors Test A & B (*M, SD*) | 17.5 (2.5) | 19.7(2.8) | *t*(57)=-3.33 | .002 |

*Note. M* = mean, *SD* = standard deviation, *Mdn* = median, m = males, f = females.
a One participant did not finish the NART.
b Product of the Block Span and the number of correctly repeated sequences.
c Education level was assessed using 7 categories in accordance with the Dutch educational system (1 = less than primary school; 7 = academic degree).

## Neuropsychological Measures

A brief battery of neuropsychological tests included: the MoCA to assess general cognitive functioning, the Dutch version of the National Adult Reading Test (NART) to estimate IQ (Schmand, Lindeboom, & Van Harskamp, 1992), the Corsi Block-Tapping Task for visual working memory (Corsi, 1973; Kessels, van den Berg, Ruis, & Brands, 2008), and from the Doors and People test the Doors test, part A and B, to test visual recognition (Baddeley, Emslie, & Nimmo-Smith, 1994). Older adults had a higher estimated IQ, whereas they performed worse than younger adults on standard clinical test measuring working memory and recognition (see Table 1), indicating an age-associated difference in memory performance.

## Experimental Tasks

### N-back

During the *N*-back task participants identify stimuli that are identical to a stimulus presented *N* trials before, in a sequence of serial presentations. Previous research showed consistent age effects on the 2-back task, in contrast to the 0-back and 1-back conditions (Daffner et al. 2011; Meissner, Keitel, Südmeyer, & Pollok, 2016). Studies comparing 1-back, 2-back and 3-back conditions show an interaction between age and task load that is driven by a smaller or no difference in 1-back

performance and although performance on the 3-back condition is lower compared to the 2-back condition the effect is to the same extent for younger and older adults (e.g., Heinzel et al., 2014; Mattay et al., 2006; Missonnier et al., 2011). We only included a 2-back version in our design, as it is hypothesized that if working memory capacity is exceeded, brain areas associated with long-term memory are recruited (Jeneson & Squire, 2012). Long-term memory involvement during the working memory task would result in overestimation of a potential correlation between visual working memory and incidental episodic memory.

The task was laptop-based and programmed using MATLAB_R2015a. Participants were seated at 50 cm from the screen. Stimuli were 50 easy-to-name objects selected from a database with colored pictures from the Snodgrass and Vanderwart's object set (Rossion & Pourtois, 2004). Equal numbers of objects from the following categories were used: toys, body parts, tools, furniture, instruments, transport, nature, fruits, insects, and clothing. The objects were presented in each of the 4 corners of the screen, in the center of the quadrant on a white background; the size of the objects was 325×325 mm. Presentation time was 500 ms followed by an interstimulus interval of 1500 ms. A schematic overview of the task is represented in Figure 1. Participants responded to targets by pressing the left button of the mouse, on nontarget trials they gave no response. In case of physical limitations participants could also respond verbally. The task consisted of 5 blocks of 20 trials with 4 targets (20%) per block and a self-paced break between the blocks. Every object was presented twice within the same block and the second presentation was always in the same location as the first. The presentation order was pseudorandom: a random sequence of numbers was generated by MATLAB to determine the presentation sequence. After this procedure the sequence was fixed to make sure that differences in performance between participants could not be due to differences in presentation order resulting in variation in amounts of lures or differences in similarity of successive objects. Instructions were given orally with support of paper-based examples; instructions were repeated on the laptop screen before starting the task. The instructions read: "You will see a sequence of objects. Each object is presented in one of the four corners of the screen. Every object will appear twice. Please only respond when the object matches the one two trials earlier, so with one other item in between. The second appearance of an object is always on the same location as the first, irrespective from whether you have to give a response or not." Four types of responses were possible: hits, misses, false alarms and correct rejections. How well participants could discriminate targets from nontargets was expressed as A-prime (*A'*), a measure suitable for tasks with high hit rate and low false alarm rates (Pollack & Norman, 1964).
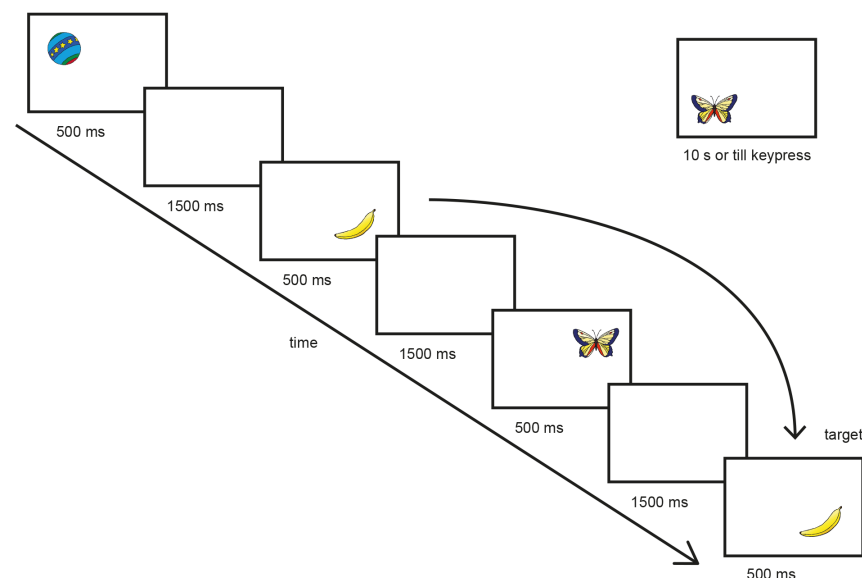
**Fig. 1.** Schematic overview of 4 trials of the 2-back task. Upper right: single trial of the subsequent memory task, in this example the correct answer is 'no' as the butterfly is now in the lower left corner, while it was presented in the upper right corner in the 2-back task.

## Subsequent memory

The 2-back task was directly followed by a surprise subsequent recognition memory test. Here, participants had to indicate whether the object was presented in the same corner of the screen now, as during the 2-back task. In order to reduce task differences, the subsequent memory task was designed as a context binding task as well, although this concerned object-location binding whereas the n-back task is by definition a temporal order binding task. The stimuli were presented until the participant responded with a maximum of 10 seconds (see Figure 1). Participants responded to every stimulus indicating whether it was in the same location (left button) or a different location (right button). When they made no response during 10 seconds the trial was noted down as a no response. All objects were presented only once in pseudorandom order. From the 20 targets of the 2-back task, half were presented in the same location as before, half in a new location. Of the previous nontargets 10 were shown in the same location as before, 20 in a new location. In total there were 20 objects in the same location, of which half previous targets, and 30 objects in a new location, presented in one block of 10 trials and two blocks of 20 trials. Similar to the 2-back task, performance was calculated as *A'*.

## Procedure

Participants completed the experiment individually after providing informed consent. A brief interview on demographics was followed by the neuropsychological measures and the experimental tasks. Instructions were standardized and the order of the tasks was fixed: the MoCA, the NLV, the Corsi Block-Tapping Task, the Doors, the 2-back task and the subsequent memory task. The total duration varied between 50 to 60 minutes.

## Analyses

In line with previous studies on associative binding we report *A'* as main outcome measure (e.g. Chalfonte & Johnson, 1996; Naveh-Benjamin et al., 2003; Peterson & Naveh-Benjamin, 2016) and $B''_D$ for response bias (e.g. Bender et al., 2010). In *N*-back literature the use of signal detection parameters *d'* and *C* is more common (Redick & Lindsey, 2013), but *A'* has been reported as *N*-back measure in a patient study (Newsome et al., 2007). *A'* is a nonparametric measure of sensitivity with scores typically ranging from 0.5, which is chance performance, to 1, which corresponds to perfect performance (Pollack & Norman, 1964; Stanislaw & Todoroc, 1999). To express response bias, non-parametric measure $B''_D$ was used, because this measure of bias is sensitive in cases of lower recognition performance, as is the case in the subsequent episodic memory task (Donaldson, 1992). $B''_D$ ranges from -1 to +1 with values less than 0 indicating a bias toward responding with yes resulting in more hits/false alarms.

To answer the question whether working memory and episodic memory performance show similar age-associated differences, we first tested whether performance on both experimental tasks in each group separately was significantly above chance level with a one-sample t-test with test value 0.5. An interaction effect was tested with a 2 × 2 (Age [younger adults, older adults] × Task [2-back, subsequent memory]) repeated measures ANOVA. Effect sizes ($\eta_p^2$) were computed for each factor to describe the proportion of variance explained. Subsequent independent sample t-tests were used to investigate the effect of age group on each of the tasks separately concerning both performance (*A'*) and response bias ($B''_D$).

To investigate how working memory performance and episodic memory performance relate in younger and older adults, Pearson correlations were calculated: overall, and for each of the two age groups separately. By means of bootstrapping a confidence interval for the correlation was determined as this method does not assume normally distributed data.

To investigate possible differences in response patterns in older and younger adults on the working memory task, hit rate and false alarm rate on the 2-back task were compared between the two age groups using Mann-Whitney U tests, given

the skewed distribution (i.e., a high number of hits and relatively few false alarms). To investigate the response patterns further, errors were identified at trial-level to test whether older adults were more sensitive to lures. Lures could be of two types, too close by (1-back, 3 trials) or too far back (4- or 5-back, 8 trials). As the sequence was determined randomly, it is by coincidence that there were no 3-back lures. A third type of error that was analyzed concerns misses on targets preceded by another target (3 trials). First, the accuracy on lures versus other nontargets, and successive targets versus other targets was calculated for older adults and younger adults. This was calculated by the total number of errors on each type of trial divided by the total number of possible errors on that trial type. Mann-Whitney U tests were performed to test for differences between the groups. Second, the percentage of a specific type of false alarm or miss to the total number of false alarms or misses at individual level was calculated to correct for the total number of errors an individual made. This second analysis was performed to take into account that some individuals make large numbers of errors in general, while we were interested in susceptibility to specific errors.

Response patterns on the subsequent memory task were analyzed to gain insight into the transition from working memory to episodic memory in younger and older adults. We analyzed the accuracy on the subsequent memory task for the 20 items that were targets in the working memory task. Targets to which the participant responded correctly (hits) in the 2-back task were compared with targets that were missed. To illustrate, when a participant had 16 hits and 4 misses in the 2-back task, accuracy in the subsequent memory task on those 16 hit items was assessed by the percentage of correct responses (either 'yes' when an item was in the correct location, or 'no' when the item was in another location) this was then compared to the accuracy in the subsequent memory task for items that were missed in the 2-back task. Interaction between responses on the 2-back task and age group was tested with a 2 × 2 (Age [younger adults, older adults] × Accuracy on the subsequent memory task for 2-back targets [2-back hits, misses]) repeated measures ANOVA.

Finally, performance on the experimental tasks is related to standard clinical tasks, namely the Corsi Block-Tapping Task, the Doors Test and the MoCA, by calculating Pearson correlations. All tests are two-tailed unless specified differently. Bonferroni correction was applied to correct for multiple testing.

## Results

### Do working memory and episodic memory performance show similar age differences when using the same stimuli?

To rule out a ceiling effect on the 2-back task, a one sample t-tests with test value 1 showed that both groups performed significantly different from the theoretically maximum score (older adults $A'$ = .92, $SD$ = .05; $t(28)$ = -8.60, $p < .001$; younger adults $A'$ = .96, $SD$ = .03; $t(29)$ = -7.46, $p < .001$). To control for chance level performance on the subsequent memory task, a one sample t-test with test value 0.5 showed that both groups performed significantly above chance level (older adults $A'$ = .71, $SD$ = .11; $t(28)$ = 10.25, $p < .001$; younger adults $A'$ = .76, $SD$ = .11; $t(29)$ = 13.04, $p < .001$). There were two outliers performing more than 2 standard deviations below the group mean, both (age 75, male, education level 6; age 26, male, education level 6) performed at chance level on the subsequent memory task ($A'$ = .36, $B''_D$ = -.31; $A'$ = .47, $B''_D$ = -.44).

To analyze performance of both groups on both tasks a repeated measures ANOVA was performed, results are shown in Figure 2. There was no significant
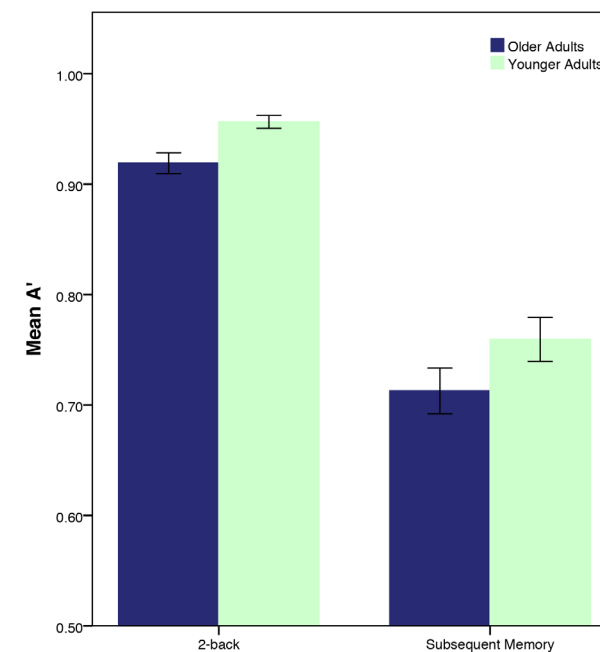


**Fig. 2.** Mean performance expressed as $A'$ (+/- 1 standard error) for older adults and younger adults, on left the 2-back task and on the right the subsequent memory task.

group by task interaction, $F(1, 57) = .09$, $p = .763$. The main effect of task was significant, with better performance on the 2-back task ($A' = .94$, $SD = .05$) than on the subsequent memory task ($A' = .74$, $SD = .11$), $F(1, 57) = 171.09$, $p < .001$, $\eta_p^2 = .75$, as was the main effect of group, where younger adults performed better than older adults, $F(1, 57) = 7.47$, $p = .008$, $\eta_p^2 = .116$.

There was no significant difference in response bias between older and younger adults on either of the tasks (2-back: older adults $B''_D = .49$, $SD = .60$; younger adults $B''_D = .55$; $SD = .53$; $t(57)=-.44$, $p = .663$; subsequent memory task: older adults $B''_D = -.03$, $SD = .36$; younger adults $B''_D = .02$; $SD = .40$; $t(57)= -.47$, $p = .637$). In the working memory task there was a tendency towards not responding while there was no preference for answering *yes* or *no* in the subsequent memory task. Removing the two outliers did not result in different findings.

## How are working memory performance and episodic memory performance related in younger and older adults?

To investigate how working memory performance and episodic memory performance relate, Pearson's correlations were calculated. As the Pearson product-moment correlation is sensitive to outliers the two participants with chance-level performance were excluded from the analyses. Overall, performance on the 2-back task was not significantly related to subsequent memory performance ($r = .174$, $N = 57$, $p = .196$). In older adults, no significant correlation was found ($r = -.182$, $N = 28$, $p = .355$), while in younger adults 2-back and subsequent memory performance correlated significantly ($r = .504$, $N = 29$, $p = .005$, Figure 3). Confidence intervals based on bootstrapping show that in older adults the interval included zero, while in younger adults both the lower and upper bound are positive. The intervals do not overlap (older adults -.548 to .185; younger adults .270 to .745).

## Are there age related differences in response patterns?

*2-back task.* Comparing the total number of hits and false alarms between the two age-groups showed that older adults had a tendency toward fewer hits ($Mdn = 16$ versus 18) and a nonsignificant difference in false alarms ($Mdn = 3$ versus 1.5) on the 2-back task ($U = 283.0$, $p = .020$; $U = 308.0$, $p = .051$, respectively) after Bonferroni correction (adjusted $\alpha = .0125$).

For further investigation of errors on the 2-back task, the effect of lures and successive targets was analyzed (Table 2). The only significant difference between older adults and younger adults was a lower accuracy on singular targets in older adults ($Mdn = 76.5\%$ versus 88.2%), $U = 256.5$, $p = .006$. The difference between the two groups in accuracy on 5-back lure trials and other nontargets trials did not survive correction for multiple testing (adjusted $\alpha = .007$). There was no significant effect of age on accuracy on successive targets, and 1-back, 4-back and total lures.
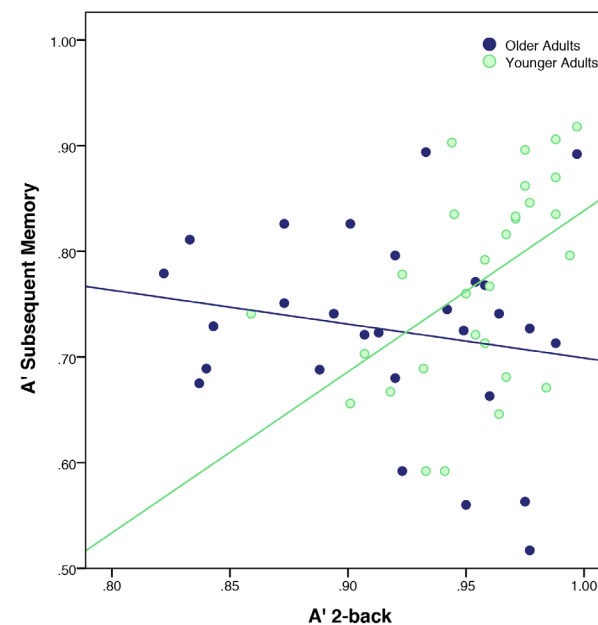


**Fig. 3.** Correlation between performance on the 2-back task (x-axis) and the subsequent memory task (y-axis) with regression lines for older adults ($r = -.182$) and younger adults ($r = .504$).

**Table 2** Median percentage of correct responses on different trial types for the total group, each age group separately and a Mann-Whitney U test for differences between the age groups.

| | | Total | OA | YA | Mann-Whitney $U$ test | |
|---|---|---|---|---|---|---|
| | | | | | $U$ | $p$ |
| Hits | Successive targets | 66.7 | 66.7 | 83.3 | 403.0 | .597 |
| | Singular targets | 88.2 | 76.5 | 88.2 | 256.5 | .006 |
| Correct rejections | 1-back lures | 100.0[a] | 100.0 | 83.3 | 400.5 | .556 |
| | 4-back lures | 100.0 | 50.0 | 100.0 | 400.5 | .554 |
| | 5-back lures | 83.3 | 83.3 | 100.0 | 307.0 | .036 |
| | Total lures | 81.8 | 81.8 | 86.4 | 342.5 | .150 |
| | Other nontargets | 100.0 | 98.6 | 100.0 | 291.5 | .017 |

*Note.* Adjusted alpha = .007 (.05/7). OA = older adults, YA = younger adults
[a] An individual score of 100% indicates that all of the trials of that type were correctly responded to.

Given that older adults made more errors on the whole, analysis of the percentage of specific errors related to the total number of errors for each individual showed that there was no significant difference in types of errors older adults made compared to younger adults (Table 3).

Table 3  Median percentage of specific errors corrected for the total number of errors at individual level, for the total group and each age group separately. Differences between older and younger adults tested with a Mann-Whitney U test.

| | | Total | OA | YA | Mann Whitney *U* test | |
|---|---|---|---|---|---|---|
| | | | | | *U* | *p* |
| Misses | Successive targets | 12.7 | 10.0 | 25.0 | 302.5 | .261 |
| False alarms | 1-back lures | 14.3 | 0.0 | 33.3 | 225.0 | .049 |
| | 4-back lures | 7.7 | 7.7 | 5.6 | 323.0 | .984 |
| | 5-back lures | 20.0 | 21.4 | 7.1 | 277.5 | .362 |
| | Total lures[a] | 75.0 | 66.7 | 100.0[b] | 231.0 | .063 |

*Note.* Adjusted alpha = .01 (.05/5). OA = older adults, YA = younger adults
a  At the individual level the percentages from the different lure types sums up to the total percentage of false alarms on lure trials.
b  An individual score of 100% indicates that all of the false alarms made by that participant were on lure trials.

*Subsequent memory task.* The number of hits and false alarms on the subsequent memory task did not significantly differ between the two age-groups (*U* = 375.5, *p* = .364; *U* = 338.5, *p* = .141, respectively). The effect of correct working memory processing on transition from working memory to long-term memory was analyzed by comparing the accuracy on the subsequent memory task for previous targets of the 2-back task that were correctly identified (hits) versus 2-back targets that were missed. A repeated measures ANOVA showed that there was no interaction between accuracy on the subsequent memory task for 2-back targets by group, $F(1, 52) = .01$, $p = .939$, no main effect of accuracy on the subsequent memory task for 2-back targets, $F(1, 52) = 3.20$, $p = .079$, or of group, $F(1, 52) = 2.52$, $p = .118$.

## Discussion

The present study investigated age-associated differences in visual working memory and episodic memory and how performance relates in younger and unimpaired older adults using a task design in which working memory and subsequent recognition memory performance were measured using the same stimuli, with both tasks involving context binding. Most of the literature is based on studies investigating the effects of age differences on memory subsystems separately; assessment of working memory and episodic memory for the same stimuli within the same subjects allows investigation of the relationship between subsystems. The results show that the subsequent memory task was more difficult and older adults performed worse than younger adults but to similar extent on both tasks. Interestingly, performance on the working memory task and the subsequent memory task was related in younger but not in older adults. Analysis of errors shows that although older adults made more miss errors, they were not more susceptible to lures than younger adults in the object 2-back task. Correct identification of targets during the 2-back task had no influence on recognition of object-locations in the subsequent memory task.

In line with comparable studies by Van Geldorp et al. (2015) and Werkle-Bergner et al., (2012) our results showed that older adults performed worse than younger adults on both working memory and subsequent memory tasks with the same stimuli. We found a moderate to large effect size, and no interaction. However, some caution is warranted when drawing this conclusion. Although we aimed at designing the tasks to be similar, there are several differences that might have influenced the results. First, the working memory task required object-order binding while the subsequent memory task required object-location binding. The *N*-back task is by definition a temporal order binding task, as the object needs to be bound to a specific place in a continuous sequence. To reduce task differences the subsequent memory task was designed as a context binding task as well. Temporal order-object binding was problematic for each object appeared twice during the 2-back task. Object-location binding was the most suitable alternative, although partly different neural correlates are associated with spatial and temporal order source memory (Ekstrom, Copara, Isham, Wang, & Yonelinas, 2011).

For two reasons we believe that the influence of these different types of context binding is limited. Previous studies have shown that temporal order-object and object-location binding are highly comparable in the way they are affected by aging, a meta-analysis showed comparable effect sizes (*d* = .99, *d* = .94; Old & Naveh-Benjamin, 2008). Furthermore, in Van Geldorp et al. (2015) the same type of binding was used in the working memory and subsequent memory task, in both studies pairs of a house and a face needed to be remembered. Overall, their results are comparable to ours, no interaction was found.

The second difference between the two tasks used in the current study concerns the encoding instructions. The working memory task with intentional instructions was followed by an unexpected subsequent memory task. The meta-analysis by Old and Naveh-Benjamin (2008) showed that the effect of age was more pronounced under intentional instructions. However, a recent study indicates that at least part of the effect might not be explained by encoding instructions, but by differences in salience and complexity of stimuli used in different experiments (Bender, Naveh-Benjamin, Amann, & Raz, 2017). Bender et al. (2017) showed that older adults only showed a disproportionate deficit for face-name associations when the face stimuli were more complex, but not when standardized greyscale faces without visual context were used. As the same stimuli appeared in both of our tasks, they do not differ in salience. The difference in performance due to intentional and incidental instructions might be limited. Moreover, intentional instructions would have resulted in the working memory task becoming a dual task in which case working memory and long-term memory would be entwined and assessing the relationship between the two systems would be unreliable. However, we acknowledge that this limits our conclusions to incidental associative episodic memory. A third difference between the working memory and subsequent memory task is the timing. In the 2-back task, participants had to respond within 2 seconds, whereas in the subsequent memory task, participants had 10 seconds to answer. It is possible that the time constraint negatively influenced especially the performance of older adults on the working memory task, as a slowing-down of processing speed is a common hypothesis to explain age-related cognitive decline (Salthouse, 1996). However, this seems unlikely as a 2 second inter-stimulus interval is common in *N*-back tasks and generally no age-related differences are reported in 1-back conditions, indicating that 2 seconds is long enough processing time for older adults for these kinds of tasks.

Of further note is the issue of potential ceiling effects that may have influenced our results. While the 2-back performance for both groups is indeed high, the performance statistically differs from the theoretical maximum score, making a ceiling effects less likely (as there is room for improvement in both groups). Still, one could argue that because of this, the overall variance in subsequent memory performance is greater than in the working memory condition, potentially obscuring an additional decline in episodic memory performance in the older adults. However, the analysis of variance takes differences in variance across groups and measures into account. Based on this, we argue that our findings are reliable, but also stress the need for replication of our results in future studies.

Concerning theories on memory decline, our results are in line with the associative deficit hypotheses that predicted similar age differences in both

memory systems. The irrelevant information hypothesis predicted, in this specific design, a possible advantage for older adults on the subsequent memory task, which we did not find. Previous studies (Campbell, Grady, Ng, & Hasher, 2012; Rowe, Valderrama, Hasher, & Lenartowicz, 2006) have shown that younger adults were able ignore irrelevant information more effectively than older adults resulting in better working memory performance but worse performance when the irrelevant items were subsequently tested, whereas older adults showed the reversed pattern. The main difference between previous studies and the current study is that the irrelevant information was tested separately from the target items (e.g., letters superimposed on line-drawings), while in the present task the object was in a specific location. This required binding of an object to a location while in previous designs no binding was required and only the distracters were tested subsequently. The only previous study that we are aware of that assessed this effect in the context of binding is Campbell et al. (2010). They found that older adults were able to encode the co-occurrence of the target- and distractor stimuli from a previous task and use this information in a subsequent task. However, in their design participants were not aware of the connection with the incidental learning task, so the effect was based on implicit memory, as opposed to explicit memory in our design. The current study shows that older adults do not show hyper-binding for irrelevant locations of objects in a way that they can explicitly use it for recognition memory. Future studies should further investigate under which circumstances older adults do benefit from irrelevant information.

The second issue we addressed was how working memory and episodic memory performance relate. An interesting finding is the significant correlation between working memory and episodic memory performance in younger, but not older adults. Given that there was no interaction between task and age-group, and that the correlation between the tasks was only significant in younger adults, we conclude that some of the older adults showed specific lower performance on the working memory task, while others showed more pronounced lower performance on the subsequent memory task, resulting in a main effect of age-group. However, it should be noted that the performance on both tasks was preserved in some older adults, two of whom even performing better than younger adults on both tasks. A possible interpretation, albeit a speculative one in the absence of neuroimaging data, is that while working memory and episodic memory are both affected by age, individual variability arises from the extent of atrophy of the underlying brain networks at an individual level, respectively the fronto-parietal network for working memory and the medial-temporal lobe for episodic memory (Maillet & Rajah, 2014 and Rottschy et al., 2012). For instance, a longitudinal study showed that age-related brain shrinkage on average affected both these regions to a similar extent, but showed profound differences at an

individual level (Raz et al., 2005). This may explain the lack of correlations between the performance on the two tasks in our study. Multiple factors may underlie individual variability in volume loss like physical activity, nutrition, hypertension and genetics (Fjell & Walhovd, 2010).

Concerning the response patterns of older and younger adults, investigation of accuracy on the working memory task showed that, as expected, more errors were made on successive targets compared to singular targets and on lure trials compared to nonlure trials (Gray, Chabris, & Braver, 2003; Kane, Conway, Miura, & Colflesh, 2007). Differences in performance between the age groups were driven by a lower hit rate in older adults. Interestingly, closer inspection revealed that older adults are not more susceptible to lures than younger adults in an object 2-back task. This finding is at odds with Schmiedek, Li, and Lindenberger (2009) who reported lower accuracy in older adults on 3- and 4-back lures. A possible explanation for this may be that our task did not include 3-back lures and that the type of stimuli differs from Schmiedek et al. (2009): black dots in a 3×3 grid versus common, easy to name objects. Common objects might provoke a stronger familiarity effect, as memory for objects is generally better than for locations (e.g., Kessels et al., 2007). A stronger effect of familiarity might explain that younger adults are also susceptible to lures.

In order to investigate whether successful episodic memory formation requires successful processing in working memory, we compared episodic memory performance on previous targets of the 2-back task comparing accuracy for objects that were correctly identified (hits) and objects that were missed during the working memory task. Neither a difference in accuracy was found, nor an age-effect. In contrast to Werkle-Bergner et al., 2012, the current study suggests that correct working memory identification does not enhance episodic memory encoding. However, an alternative explanation is possible. Working memory tasks generally consist of three phases with different contributions to long-term memory formation: encoding, maintaining/updating and testing (Bergmann, Kiemeneij, Fernández, & Kessels, 2013). Part of the maintaining phase is the transformation from perceptual representation to internal code, which is thought to be crucial for episodic memory formation (Bergmann et al., 2013). The maintaining phase is similar for all stimuli in our working memory task, which might explain why performance on the working memory task did not influence episodic memory recognition. In the task used by Werkle-Bergner and colleagues (2012) a cue was presented before stimulus presentation to indicate whether the item needed to be remembered or not, possibly resulting in differential encoding explaining the different findings.

In sum, previous studies have investigated the performance of younger and older adults on different working memory and episodic memory tasks, concluding that both systems show age-related impaired performance by older adults. By using the same stimuli and addressing working memory and episodic memory in one task design, we investigated the relation between working memory and episodic memory performance. We conclude that although mean age differences are similar on these visual working memory and incidental associative memory tasks, the relationship is different for younger and older adults. That is, working memory and episodic memory were correlated in younger but not in older adults. Longitudinal research is needed to investigate life-span changes in the relationship between working and episodic memory. As some neurodegenerative diseases are characterized by specific types of memory impairment, it is important to have a profile of functioning of memory subsystems for unimpaired older adults. The combining of the *N*-back task with a subsequent memory task is found to be a fruitful approach for investigation of the relation between visual working memory and episodic memory.

# Chapter 3

Visual working memory and
episodic memory in stroke patients

## Abstract

Working memory and episodic memory are two different processes, although the nature of their interrelationship is debated. As these processes are predominantly studied in isolation, it is unclear whether they crucially rely on different neural substrates. Eighty-one adults with sub-acute ischemic stroke and twenty-nine elderly controls were assessed on a visual working memory task, followed by a surprise subsequent memory test for the same stimuli. Multivariate and atlas-based lesion-symptom mapping (LSM) analyses were performed to identify anatomical correlates of visual memory. Behavioral results gave moderate evidence for independence between discriminability in working memory and subsequent memory, and strong evidence for a correlation in response bias on the two tasks in stroke patients. LSM analyses suggested there might be independent regions associated with working memory and episodic memory. Lesions in the long segment of the arcuate fasciculus were more strongly associated with discriminability in working memory than in subsequent memory, while lesions in the posterior segment of the arcuate fasciculus were more strongly associated with criterion setting in subsequent memory than in working memory. These findings largely support the multicomponent view of memory.

## Introduction

Working memory and episodic memory are two different processes, although the nature of their interrelationship is debated. The multicomponent perspective on human memory function (e.g. Squire 2004) is based on clinical cases with specific memory deficits and has been supported by neuroimaging studies that indicated a frontoparietal network to be involved in working memory processes (D'Esposito et al. 2000; Rottschy et al. 2012), whereas the medial temporal lobe is associated with long-term memory processes (Spaniol et al. 2009; Squire 1992). In contrast, other memory models that distinguish between different processes for short-term and long-term memory do not necessarily imply different neural mechanisms but describe working memory as activated portion of long-term memory (e.g. Atkinson and Shiffrin 1971; Cowan 1988). According to this view, memory representations can be in a temporarily activated state so that they are easily accessible. This activated state is limited to items in the focus of attention.

There is accumulating evidence showing that brain regions typically associated with long-term memory, such as the hippocampus, are active during working memory and that frontal and parietal regions are active during long-term memory (reviewed in Ranganath and Blumenfeld 2005). However, only a few studies take into account that activation during a working memory task might actually reflect long-term memory formation rather than working memory processing. The studies that do, report mixed results concerning parahippocampal and hippocampal involvement in working memory processes (Axmacher et al. 2008; Bergmann et al. 2015; Bergmann et al. 2016; Zanto et al. 2015).

The key distinction between the multicomponent view of memory and the activated long-term memory view is the need for a separate copy of information, or a set of temporary pointers to relevant long-term memory, in a distinct working memory store (D'Esposito and Postle 2015; Baddeley et al. 2019; Cowan 2019; Norris 2017; Norris 2019; Oberauer 2009; Shallice and Papagno 2019). As working memory and episodic memory are predominantly studied in isolation, it is unclear whether they crucially rely on different neural substrates. Patients with brain lesions might give insight as the two theoretical models make different predictions for patients with brain injury. According to the multicomponent model of memory, working memory and episodic memory performance can be separately affected by brain lesions and have a distinct neural profile as two separate representations are formed. Based on the theory of activated long-term memory, direct and delayed memory rely on the same representations. Therefore, neural correlates of working memory and episodic memory are expected to partly overlap. Two behavioral profiles fit this theory of activated long-term memory. One, impaired performance on both the working memory and episodic memory task due to a

failure in rapid new learning. Two, impaired performance on only the episodic memory task that can be explained by a failure to consolidate information due to time-based decay or interference.

To date, no study directly compared patients with lesions on working memory and long-term memory processing. We thus employed an *N*-back task with easy to name stimuli to assess working memory (Lugtmeijer et al. 2019). In this way we avoided the processing of complex stimuli which might engage long-term memory processing even when the retention interval is short (Jeneson and Squire 2012), without inducing a ceiling effect (Axmacher et al. 2008) that might arise from a match-to-sample design with simple stimuli. The *N*-back task was followed by an unexpected subsequent memory task in which participants had to indicate whether an object is on the same location of the screen as during the *N*-back task. The encoding phase is the same for both tasks as encoding takes place during the first presentation of the object during the working memory task. During this first presentation an object is bound to both serial order and spatial location. Working memory performance is based on maintenance of this bound information for object and order, while performance on the subsequent memory task is based on recollection of spatial information bound to an object.

Our first goal was to determine how working memory and episodic memory performance are related in an unselected cohort of stroke patients. Our second goal was to investigate unique and shared lesion locations associated with working memory and episodic memory. We used multivariate lesion symptom mapping and atlas-based lesion symptom mapping to identify on voxel- and ROI-level areas that contribute to memory performance.

## Methods

### Study Design

This study is part of the Functional Architecture of the Brain for Vision (FAB4V) study, a multi-center prospective cohort study on vision and cognition after ischemic stroke in adults aged 18 through 90 years. Patients were admitted between September 2015 and December 2019 to one of the following hospitals in The Netherlands: Amsterdam University Medical Center (Amsterdam UMC), Radboud University Medical Center (Radboudumc) in Nijmegen, University Medical Center Groningen (UMCG), University Medical Center Utrecht (UMCU), Onze Lieve Vrouwe Gasthuis (OLVG), Maasziekenhuis Pantein, Rijnstate, Ommelander Ziekenhuis Groep, St. Antonius Ziekenhuis, and Diakonessenhuis. Assessment took place at one of the four academic hospitals. The Medical Review Ethics Committee Utrecht approved the study (30-06-2015), and written informed consent was obtained from all participants prior to participation.

Patients were identified based on their medical records at admission to the hospital and in consultation with their treating neurologist or nurse practitioner approached for participation. Ischemic stroke was defined as focal neurological deficit persisting >24 hours. Inclusion criteria: diagnosis of ischemic stroke made by an expert neurologist, age between 18 and 90, sufficient Dutch language skills to understand task instructions. Exclusion criteria: hemorrhagic stroke, cerebral venous sinus thrombosis, pre-existing cognitive decline (IQCODE score > 3.6) or dementia, pre-existing visual impairment, psychiatric disorder and severe aphasia. Examination took place between 2 weeks and six months post stroke.

Patients that participated between July 2016 and March 2019 at the Radboudumc, Amsterdam UMC, and UMCG were recruited for the memory subgroup. These patients were tested more extensively on memory than the standard neuro-psychological assessment of the cohort study.

A stroke-free, aging, control group existed of 29 adults, aged 62 to 90 (*M* = 72.1, *SD* = 6.8, 13 men). There was no difference in level of education ($t(107) = 1.19$, p = .24). Controls had no history of neurological disease or cognitive decline. Controls were recruited from social networks and received monetary compensation for their participation.

### Memory assessment

To assess visual working memory, an *N*-back task with common objects was employed (for more details on the task see Lugtmeijer et al. 2019). In short, during the 2-back task, stimuli are presented in serial presentations and participants identify stimuli that are identical to a stimulus presented 2 trials before. This requires temporal-order binding. Stimuli were 50 easy-to-name objects that were presented in each of the 4 corners of the screen. Presentation time was 500 ms followed by an interstimulus interval of 1500 ms. A schematic overview of the task is represented in Figure 1. The task consisted of 5 blocks of 20 trials with 4 targets (20%) per block. Every object was presented twice within the same block and the second presentation was always in the same location as the first. Participants responded only to targets by pulling a joystick towards them. In case of physical limitations participants could respond verbally.

Directly following the 2-back task participants completed a surprise subsequent recognition memory test for assessing episodic memory function. Here, participants had to indicate whether an object was presented in the same corner of the screen now, as during the 2-back task. All objects from the 2-back were presented once, no new items were added. Out of 50 objects, 20 were presented at the same location as before (targets). This task relies on visuospatial binding. The stimuli were presented until the participant responded, within a limit of 10 seconds (see Fig. 1).
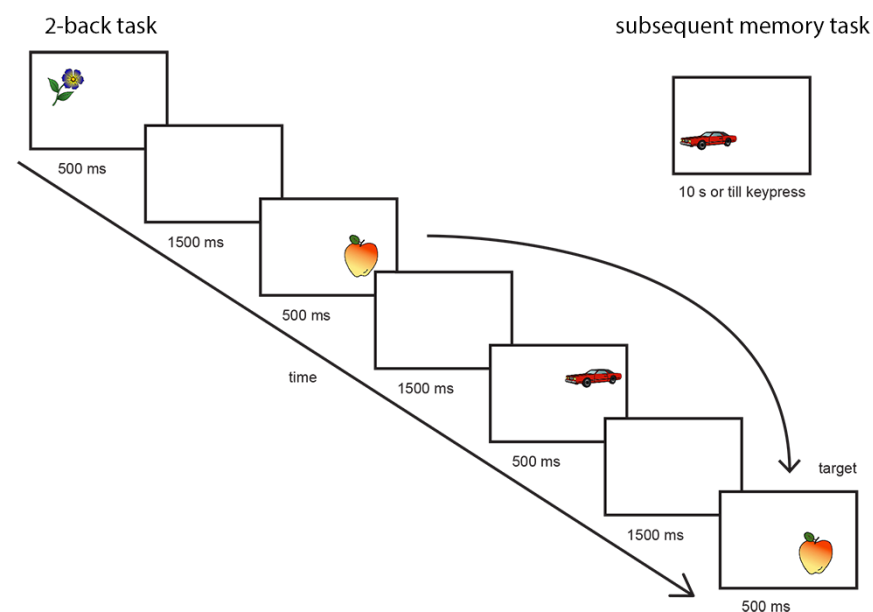
**Fig. 1**. Task design. 2-back task from left to right. In the upper right corner a stimulus example from the subsequent memory task in which the correct answer is "false" as the car in is the lower left corner while it was in the upper right corner during the 2-back task.

For both tasks four types of responses were possible: hits, misses, false alarms, and correct rejections. How well participants could discriminate targets from nontargets was expressed as d-prime (*d'*), higher scores indicate better performance. Response criterion (*c*) reflects an overall preference to answer yes (target) or no (non-target). Positive values indicate a conservative response bias, while negative values reflect a liberal response bias.

### Imaging data acquisition

Participants underwent a 3-T magnetic resonance imaging scan, at the Radboudumc and UMCG on the Siemens Magnetom Prisma, at the Amsterdam UMC and UMCU on the Philips R5. For the Siemens scanner, sequence details were as follows: T2 FLAIR (TI = 1650ms, TR = 4800ms, TE = 484ms, [FOV] = 280mm, voxel size 0.9×0.9×0.9mm$^3$). For the Philips scanner, sequence details were: T2 FLAIR (TI = 1650ms, TR = 4800ms, TE = 253ms, [FOV] = 250mm, voxel size 1.12×1.12×0.56mm$^3$).

### Lesion segmentation and preprocessing

Lesions were delineated semi-automatically or fully manually in native space using ITK-snap software (Yushkevich et al. 2006) on the axial slices of the FLAIR, checked in sagittal and coronal directions. Hyper-intensities surrounding the lesion indicating additional white matter degeneration and gliosis were included as a part the lesion. Lesions were delineated by three researchers. To check for interrater reliability four scans (5%) were randomly selected and lesions were delineated by the researchers independently. A score was calculated as the percentage of voxels selected by all three, two or one rater, in reference to the number of voxels being selected by at least one rater. The mean percentage over overlap for all three raters was 75.6% (range 69.8% - 83.2%), two raters agreed on 82.4% (range 74.2% - 90.8%). In case of doubt for specific scans, a neurologist or radiologist was consulted.

The FLAIR and binary lesion mask were normalized to an older adult MNI template using the unified segmentation/normalization algorithm implemented in SPM12 (Crinion et al. 2007; Rorden et al. 2012). For unilateral lesions, enantiomorphic normalization was applied as this method has been shown to be vastly superior to cost function masking (Nachev et al. 2008). For bilateral lesions cost function masking was applied. Normalisation was inspected for all individuals by visually comparing the normalized lesion mask overlaid on the FLAIR in MNI space to the lesion mask and FLAIR in native space. Segmentations in MNI space were manually corrected when necessary.

### Multivariate Lesion Symptom Mapping

Multivariate LSM analyses were performed using support vector regression (SVR-LSM) (Zhang et al. 2014) with a toolbox that allows for the adding of covariates and different lesion volume correction methods (DeMarco and Turkeltaub 2018). Multivariate LSM has a higher sensitivity and specificity for detecting the lesion-behavior relations by considering intervoxel correlations compared to univariate lesion-behavior mapping methods (Zhang et al. 2014). Settings of hyperparameter values, with a cost of 30 and gamma of 5, were kept in line with recommendations from the original publication (Zhang et al. 2014). Analyses were conducted with and without lesion volume correction. Lesion volume was corrected for by regressing lesion volume on the behavioral scores and lesion data in each voxel. This was based on recommendations by DeMarco and Turkeltaub (2018), who showed that regressing lesion volume on both is most effectively addressing the bias of lesion volume without being overly conservative, while at the same time being more strict than the commonly used method of direct total lesion volume control (dTLVC). Only voxels that were lesioned in a preset number of participants are included in the analyses, a correction known as

'sufficient lesion affection'. In accordance with previous studies, we set the threshold at 5% of the whole sample (Sperber and Karnath 2017), which translates to voxels lesioned in at least four participants. Permutation testing (10,000 permutations) was used for testing statistical significance for the β values, with a voxelwise threshold of $p < .005$, and a clusterwise threshold of $p < .05$, only including clusters larger than 50 voxels. Age and education level (scored in categories based on the Dutch educational system, range 1-7, low to highly educated; Verhage 1964) were regressed out from the behavioral scores and lesion data.

### Atlas-based Lesion-Symptom Mapping

For atlas-based LSM the statistical lesion analysis software NiiStat was used (https://github.com/neurolabusc/NiiStat). The atlas-based analysis we used relies on the cumulative lesion burden in a specific region, instead of investigating lesions on a voxel-wise basis. This has the advantage of effectively increasing the number of areas that have sufficient coverage across participants, assuming that lesions in nearby voxels affect behavior in the same way. In addition, univariate voxel-wise LSM is conservative due to strict multiple testing corrections, in a ROI-based approach this effect is reduced. For white-matter regions of interest (ROIs) we used the CAT atlas containing 32 ROIs (Catani and De Schotten 2008; https://www.natbrainlab.co.uk/). For gray-matter, ROIs the corrected Glasser atlas that defines 380 ROIs was used (Glasser et al. 2016; https://identifiers.org/neurovault.collection:1549). Analyses were conducted with and without lesion volume correction. Lesion volume control in NiiStat is based on regressing the lesion volume with the behavioral variable. We adapted the code to be able to regress lesion volume on both the behavioral scores and ROI-based lesion data, in line with our multivariate LSM analysis. Only ROIs included in the lesion masks of at least four participants were analysed. Permutation testing to correct for multiple testing, was set to 10,000 permutations at $p > .05$. Age and education level were included as covariates and the toolbox was adjusted to regress these on the behavioral and lesion data. To test if effects were specific for the working memory or subsequent memory task, the performance on the other measure was included in a subsequent analysis as covariate.

### Statistical analyses

To test how representative our memory subgroup was for the total cohort we tested for group differences in baseline characteristics between patients in the memory subgroup and those in the total cohort with an independent sample $t$-test, a Mann–Whitney U test, or Pearson $\chi^2$ test, when appropriate. Two-tailed $p$ values <0.05 were considered statistically significant. Performance on the experimental

tasks was compared to an aging, stroke-free, control group with independent sample $t$-tests.

Associations between working memory and episodic memory performance, and performance and lesion volume, were tested with partial correlations (Pearson's $r$), adjusting for age and education level. Bayesian pairwise correlations were used to test the strength of the support for the null-hypothesis or alternative hypothesis. An ANOVA with age and education as covariates, was used to test the difference between patients and controls on discriminability and criterion in working memory and episodic memory. The association between lesion volume and behavioral measures was assessed with correlations. Before computing the correlations, variance due to age and education was regressed out of the behavioral measures and lesion volume. Because lesion volume was not normally distributed, the significance of these correlations was assessed by permutation testing with 1000 permutations, in line with the LSM analyses. For criterion, both positive and negative values indicate a larger response bias and therefore less optimal response patterns. The value 0 indicates no bias, positive values indicate a conservative bias and negative values a liberal bias. Therefore, we first tested whether lesion volume was associated with a larger response bias, independent of direction, by using the absolute values of criterion. Only if that was the case, we tested the direction of the effect by using the continuous measure of criterion. This same two-step procedure was applied in the LSM analyses. To test for specific deficits, we selected patients with scores 2 SD below the control group mean for each memory task and investigated how many of patients performed low on both tasks.

## Results

### Participants

Of 289 patients included in the cohort, a subset of 105 was recruited for participation in the memory study, the memory subgroup. Twenty-four patients were excluded from all analyses due to no MRI ($N$ = 4), no FLAIR sequence ($N$ = 8), or no lesion visible ($N$ = 12). This resulted in a final sample of 81 patients. Patients in the memory subgroup did not differ from other patients in the cohort on descriptive variables, stroke characteristics, vascular risk factors, or memory function as measured by standard assessment (Table 1). The only difference between the patients included in the subgroup and those who were not is the number of patients with no MRI or no lesion visible on MRI, as that was an exclusion criterion.

**Table 1** Descriptives of patients in the memory subgroup and other patients in the cohort.

|  | Memory subgroup | Other patients | $p$ |
|---|---|---|---|
| No. | 81 | 208 | NA |
| Men no. (%), $\chi^2$ | 61 (75) | 138 (67) | .15 |
| Age $M$ ($SD$) [range], t-test | 59.8 (12.5) [20-89] | 61.0 (13.4) [19-89] | .46 |
| Handedness r:l:a:u, (r %), $\chi^2$ | 70:9:1:1 (86) | 171:20:5:12 (82) | .78 |
| Education $Median$ [range], $\chi^2$ | 5 [2-7] | 5 [1-7] | .84 |
| IQ estimate[1] $M$ ($SD$), t-test | 100.5 (15.8) | 103.5 (13.1) | .12 |
| HADS depression $M$ ($SD$), t-test | 3.31 (2.88) | 3.82 (3.86) | .26 |
| HADS anxiety $M$ ($SD$), t-test | 3.83 (3.17) | 4.82 (4.12) | .05 |
| Previous stroke n:y:u, $\chi^2$ | 62:13:6 | 150:46:12 | .27 |
| Hemisphere l:r:b:c:a, $\chi^2$ | 35:32:12:2:0 | 58:60:28:8:43 | <.001 |
| Hypertension no. (%), $\chi^2$ | 33 (41) | 80 (38.5) | .94 |
| Diabetes I / II no. (%), $\chi^2$ | 1 (1.2) / 10 (12.3) | 2 (1.0) / 24 (11.5) | .96 |
| Hypercholesterolemia no. (%), $\chi^2$ | 26 (32.1) | 44 (21.2) | .09 |
| Interval in days[2] $M$ ($SD$), t-test | 53.3 (26.2) | 61.4 (35.7) | .07 |

*Notes.* 1) premorbid IQ estimated with the Dutch version of the National Adult Reading Test, 2) interval between stroke and assessment
NA = not applicable, r = right, l = left, a = ambidextrous, u = unknown, y = yes, n = no, b = bilateral, c = cerebellar/brain stem, a = no MRI or no lesion on MRI

## Behavioral performance

Partial correlations were used to determine the relationship between performance on the working memory and episodic memory task, whilst controlling for age and education. In patients, there was no significant partial correlation for discriminability, $r(79) = -.02$, $p = .87$. There was a significant correlation for criterion, $r(79) = .30$, $p = .01$. Bayesian pairwise correlations corrected for age and education, based on a hypothesis of positive correlation, gave moderate evidence in favor of the null hypothesis for no correlation in discriminability, $BF_{10} = .12$, and strong support for a correlation between criterion on both tasks, $BF_{10} = 8.71$ (Jarosz and Wiley, 2014). In the control group both discriminability and criterion did not correlate ($d'$: $r(29) = -.10$, $p = .61$, $BF_{10} = .16$; $c$: $r(29) = .13$, $p = .49$, $BF_{10} = .43$, Fig. 2).

A one-way ANOVA with age and education as covariates, shows that at group-level patients had lower discriminability than controls for the 2-back task ($F(1, 106) = 5.80$, $p = .02$), but not for the subsequent memory task ($F(1, 104) = 1.63$, $p = .21$). For absolute response bias, mean scores for both groups were similar in

the 2-back task ($F(1, 106) = .31$, $p = .58$), in the subsequent memory task patients showed a stronger bias ($F(1, 104) = 4.61$, $p = .03$). This stronger response bias in the subsequent memory task is in both directions (more liberal and more conservative) as there is no difference between patients and controls for the continuous measure of criterion ($F(1, 103) = 0$, $p > .99$).
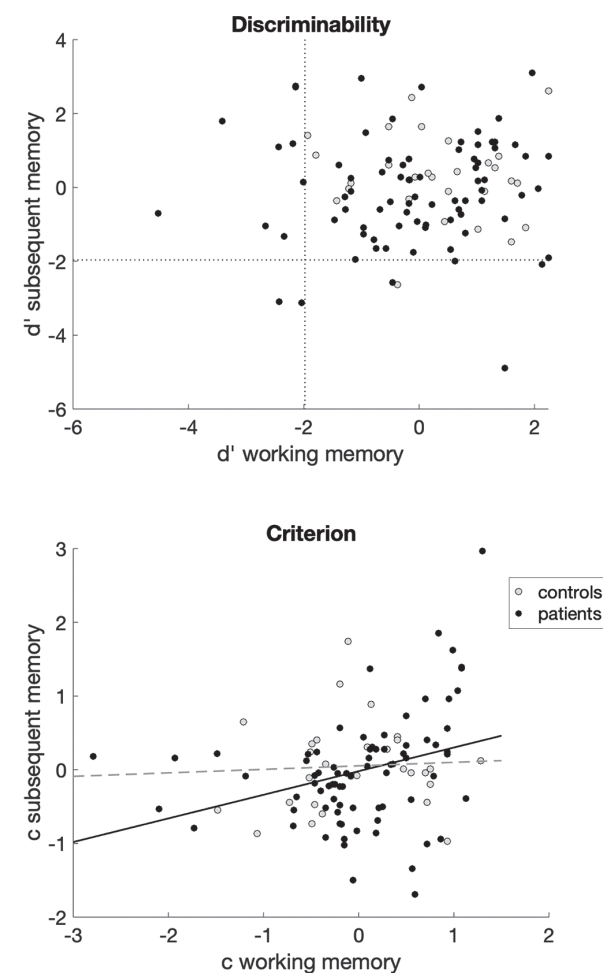


**Fig. 2.** Performance from patients (in black) and controls (in gray) with the 2-back task on the x-axis and subsequent memory task on the y-axis, a) discriminability ($d'$) with reference lines at 2 $SD$ below average performance based on the control group, b) criterion ($c$).

Further investigation to get insight in system specific deficits in patients who performed worse than average (2 *SD* below the mean of the control group) in terms discriminability, showed that nine patients only had an impairment on the 2-back task, four only on the subsequent memory task, and two on both tasks (Fig. 2).

## Lesion distribution
Median lesion volume was 5.77 cm$^3$ (range .79 – 137.49 cm$^3$). Figure 3 shows the lesion prevalence map. Voxels lesioned in at least four patients have a green, yellow or red color (Fig. 3). Lesions in the left hemisphere are as frequent as in the right hemisphere (Table 1) although median lesion size is larger in the right hemisphere (6.16 versus 3.97 cm$^3$).
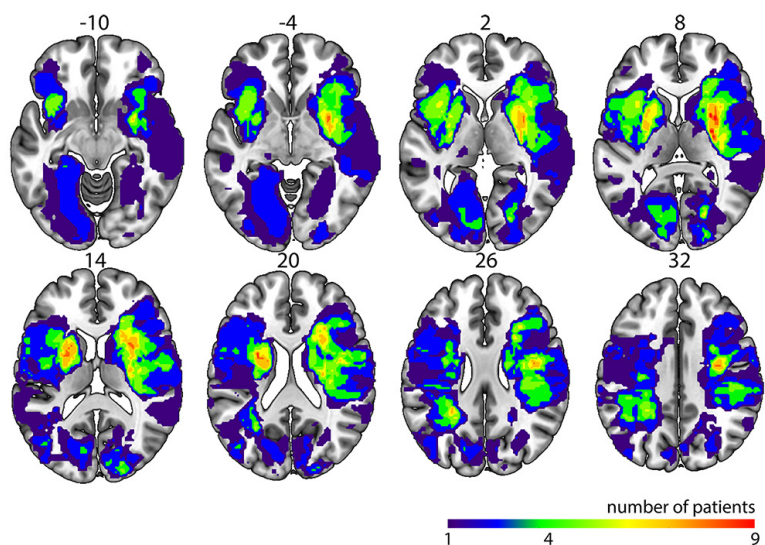


**Fig. 3.** Lesion prevalence map as an overlay on the 1mm MNI-152 template. Numbers above the slices correspond with z-coordinates in MNI space. Left hemisphere is depicted on the left. The color bar indicates the number of patients with a lesion for each voxel. Voxels that are lesioned in at least four patients, green colors and warmer, are included in the LSM analyses. Maximum overlap is 9.

The association between lesion volume and behavioral outcome measures was assessed with correlations and the significance of these correlations was assessed using permutation tests, after accounting for effects of age and education. For discriminability there was a significant association with lesion volume with the 2-back task, $r = -.22$, $p = .03$, and a correlation approaching significance for the

subsequent memory task, $r = -.18$, $p = .05$. Larger lesion volume was associated with lower discriminability. For the working memory task there was no significant association between absolute response bias and total lesion volume, $r = .12$, $p = .13$. The correlation between absolute response bias on the subsequent memory task and lesion volume was significant, $r = .37$, $p < .01$. Larger lesion volume was associated with a more conservative response bias indicated by a significant positive correlation between the continues measure of response bias and lesion volume, $r = .31$, p < .01. After exclusion of 4 patients with lesion volumes more than 2 standard deviations larger than the mean, there was no significant correlation for 2-back discriminability and criterion with lesion volume. The association between lesion volume discriminability on the subsequent memory task remained the same, $r = -.19$, $p = .05$. The absolute response criterion on the subsequent memory task correlated, as in the previous analysis, with lesion volume, $r = .31$, $p < .01$. The direction of this response bias in subsequent memory is less clear after exclusion of outliers, $r = .14$, $p = .25$.

## Multivariate Lesion Symptom Mapping
Analyses identified for discriminability on the 2-back task, a cluster that based on the CAT atlas overlaps with the anterior and long segment of the arcuate fasciculus in the right hemisphere (voxelwise theshold $p < .005$, cluster size 2032, peak voxel: x = 34, y = -26, z = 23, clusterwise $p = .02$). This effect remained significant when discriminability on the subsequent memory task was added as covariate (voxelwise theshold $p < .005$, cluster size 2032, peak voxel: x = 36, y = -24, z = 7, clusterwise $p = .02$, Fig. 4A). When lesion volume was corrected for, the association was no longer significant. For discriminability on the subsequent memory task, and criterion on both tasks, no significant clusters were identified. All analyses were controlled for age and education.

## Atlas-based Lesion Symptom Mapping
Of the 360 gray-matter ROIs included in the corrected GLASSER atlas, 111 were covered by at least 4 lesions. The white-matter CAT atlas consists of 32 ROIs out of which 28 had sufficient lesion coverage (see Supplementary materials for details). For discriminability on the 2-back task, a significant correlation was found with lesion status after controlling for age and education. Lesion status in the long segment of the arcuate fasciculus in the right hemisphere was associated with 2-back discriminability ($z = -3.26$, threshold $z < -3.15$, Fig. 4B), this effected is based on 8 patients with a lesion in this tract. This effect remained when discriminability on the subsequent memory task was added as covariate ($z = -3.25$, threshold $z < -3.22$), suggesting that lesions in this region are more strongly associated with n-back than subsequent memory discriminability.
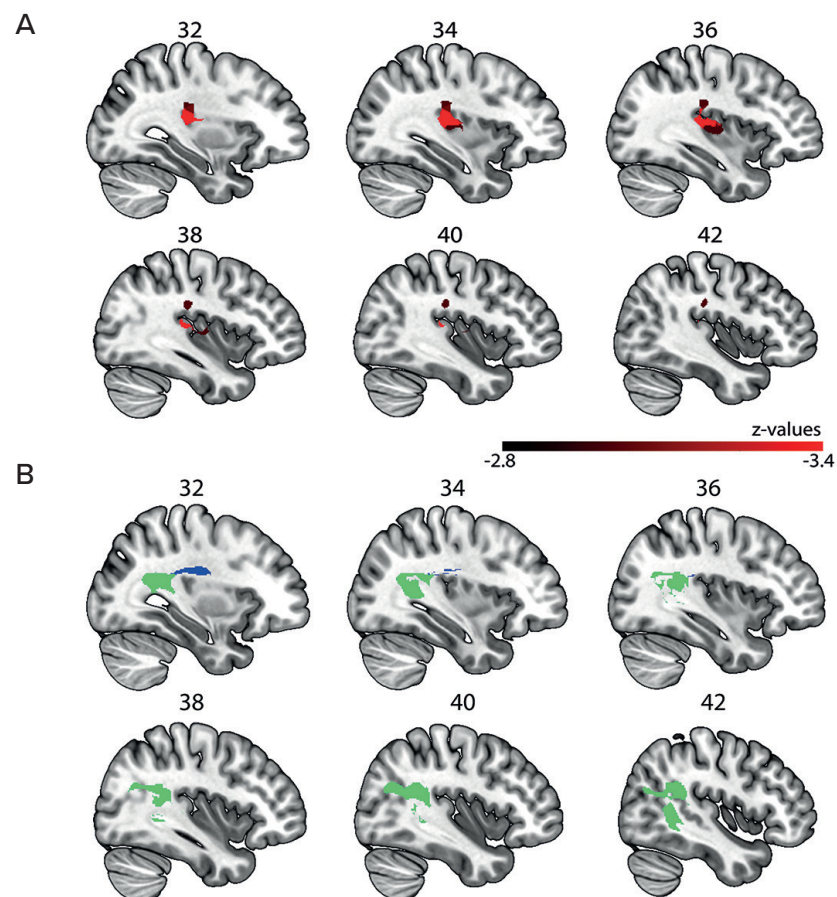
**Fig. 4. A**) Results from the multivariate LSM analysis, controlled for age, education, and performance on the other task, but not for lesion volume. **B**) Results from the atlas-based LSM analysis, controlled for age, education, and performance on the other task but not for lesion volume. The long segment of the arcuate fasciculus (in blue) is associated with discriminability on the 2-back task. The posterior segment of the arcuate fasciculus (in green) is associated with criterion on the subsequent memory task. Numbers refer to MNI coordinates. Left hemisphere is depicted on the left.

Absolute criterion on the subsequent memory task showed a significant correlation with lesion status in the posterior segment of the arcuate fasciculus in the right hemisphere after controlling for age and education ($z = 4.76$, threshold $z > 4.54$, Fig. 4B). Six patients had a lesion in this tract. The association remained significant after adding criterion on the 2-back task as covariate ($z = 4.62$, threshold

$z > 4.47$). This suggests that lesions in this region are more strongly associated with criterion in subsequent memory than in 2-back. To assess in which direction lesions in the posterior segment of the arcuate fasciculus influence response bias, the association with the continuous measure of criterion on subsequent memory was tested. Lesions in the posterior segment of the arcuate fasciculus in the right hemisphere are associated with a more conservative response bias ($z = 4.21$, threshold $z > 3.81$), also when criterion on the 2-back task is included as covariate ($z = 3.92$, threshold $z > 3.48$). Age and education level did not correlate significantly with lesion status in any of the ROIs. When controlling for lesion volume none of the associations with discriminability and criterion remained significant.

## Discussion

The aim of this study was to contrast the theory of separate memory stores with the theory of working memory as activated long-term memory, by investigating the behavioral and neuroanatomical correlates of working and episodic memory. This was possible because we used a task design in which working memory and episodic memory are assessed based on the same encoding phase. We used behavioral and neuroimaging data to investigate 1) the relation between visual working memory and episodic memory performance and 2) anatomical correlates of visual memory function using multivariate voxel-based and atlas-based approaches. We found that discriminability in working memory and episodic memory were independent at the behavioral level. In contrast, response bias was correlated between working memory and episodic memory in stroke patients. LSM analyses suggested there might be independent regions that are associated with working memory and episodic memory performance.

The key issue in the ongoing debate on the multicomponent model of memory versus the view of working memory as activated long-term memory, is the need of a separate and independent short-term memory store (Baddeley et al. 2019; Cowan 2019; Norris 2017; Norris 2019; Oberauer 2009; Shallice and Papagno 2019). According to the multicomponent model, a separate store and mechanism is needed to construct new representations and actively maintain relational information (Norris 2017, 2019). The theory of activated long-term memory states that this can be achieved by rapid new learning, in which new associations can be formed as new long-term memory trace. While the multicomponent model of memory explains long-term memory deficits as the failure to encode a representation into long-term memory, the theory of activated long-term memory interprets this as a failure of consolidation of rapidly formed new long-term memory traces (Cowan 2019). If rapidly formed representations underlie associative memory,

interference or a deficit in consolidation explains low performance on the subsequent memory task but does not explain low performance solely on the working memory task. Our results suggest that there might be separate representations in working memory and episodic memory as discriminability is not correlated between the tasks and some patients show selective impairment. Response bias on the other hand seems a shared process in working memory and episodic memory.

Results from the LSM analyses suggested there might be independent regions that are associated with working memory and episodic memory performance. Lesions in the anterior and long segment of the arcuate fasciculus in the right hemisphere were more strongly associated with discriminability in working memory than in subsequent memory, while lesions in the posterior segment of the arcuate fasciculus were more strongly associated with criterion setting in subsequent memory than in working memory. As we included the scores for discriminability and criterion on the other task as covariate, we can state that there is a stronger association for one task than for the other with lesion status in these regions. The arcuate fasciculus connects the perisylvian cortex of the frontal, parietal, and temporal lobes. In the left hemisphere the three segments of the arcuate form the perisylvian language network, which is extensively studied (e.g. Bonakdarpour et al. 2019; Catani et al. 2005). The limited literature on the right arcuate fasciculus associated lesions in this region with spatial neglect (Catani and De Schotten 2008; Machner et al. 2018), visuospatial processing (Rolland et al. 2018), visual working memory (Chechlacz et al. 2014; Matias-Guiu et al. 2018). We found discriminability on the working memory task, compared to the episodic memory task, to be stronger related to lesions in the anterior and long segment of arcuate fasciculus. Based on our results and previous findings we suggest that the right arcuate fasciculus is specifically involved in visual working memory. This is in line with a meta-analysis concerning studies of patients with traumatic brain injury that associated the arcuate fasciculus with processing speed, attention, and working memory, but not other forms of memory (Wallace et al. 2018). It is interesting to note that for criterion setting we only found an association with lesion status in the posterior segment of the arcuate fasciculus for the subsequent memory task while criterion was correlated between the tasks at the behavioral level. Even though there was strong evidence for a correlation, the correlation was weak. The correlation might be explained by a third factor influencing response bias on both tasks even if they have different neural substrates. A possible factor related to response bias is age (for a meta-analysis see Fraundorf et al. 2019). Future studies are needed to investigate specialization of different segments of the arcuate fasciculus in visual memory. The results from our LSM analyses should be interpreted with caution because the associations between memory performance and lesion location were no longer significant after correction for lesion volume. Larger

lesion volume was associated with lower discriminability and stronger response bias, this effect might be mainly driven by lesions in the anterior and long segment of the arcuate fasciculus for working memory discriminability and in the posterior segment of the arcuate fasciculus for criterion setting in episodic memory.

Our results are in conflict with a previous study in stroke patients on discriminability and criterion setting in verbal recognition memory. This study indicated that the left medial temporal lobe, left temporo-occipital structures, both thalami, and the right hippocampus are associated with discriminability, while the right inferior frontal gyrus is crucial for criterion setting (Biesbroek et al. 2015). Two main differences should be pointed out, the verbal versus visual nature of the task and the distribution of lesions. Lesion symptom-mapping studies rely heavily on the total lesion prevalence distribution resulting in differences between studies. Previous studies have shown different neural correlates for verbal and visual memory (e.g. Donolato et al. 2017), though it has also been demonstrated that both verbal and visual memory deficits are better predicted by functional connectivity than by lesion location (Siegel et al. 2016).

The advantage of studying stroke patients is that due to the sudden nature of the brain damage, it is acceptable to infer causal relations (Karnath et al. 2019; Rorden and Karnath 2004). A critical comment is that people with stroke might have a higher vascular burden that is related to memory function (Van Leijsen et al. 2019). There might be a selection bias in the sample with patients with mild symptoms and small lesions being more likely to participate in research. This has a consequence for the distribution of lesions across the brain, though this is party inherent to the population studied. Brain lesions due to stroke are determined by the vascular tree resulting in vulnerable lesion sites and intercorrelation between voxels. Even though there might be locations in the brain crucial to a specific task that are rarely affected by stroke, these would not be considered as main associates for post-stroke memory deficits. A limitation remains that we can only draw conclusions on the voxels/ROIs with sufficient lesion coverage and that some areas typically associated with memory, like the hippocampus, were not included in the analyses.

With the task design we used, we aimed to assess working memory and episodic memory in one task design, using the same stimuli, the same encoding phase and comparable binding demands. The difficulty is assessing two different processes in a comparable task with limited confounding factors differentiating between which processed is tapped into. A few limitations concerning the task design should be mentioned. First, although several studies indicate that contextual binding for time and space relies on the hippocampus (e.g. Eichenbaum 2017; Yonelinas et al. 2019), they might not have fully overlapping neural correlates. A recent study showed that different subregions within the hippocampus were

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differently associated with object-location, object-time and object-object associations in development from childhood into adolescence based on structural MRI in 171 subjects (Lee et al. 2020). Furthermore, an fMRI study of 16 healthy subjects showed activations in specific areas for spatial order (parahippocampus) and temporal order processing (Brodmann area 10 within the prefrontal cortex), in addition to general hippocampal involvement for source retrieval (Ekstrom et al. 2011). Given these results, we cannot fully rule out the possibility of stroke selectively affecting different types of binding. Second, hyper-binding might differently affect the working memory and subsequent memory task. In the ageing literature hyper-binding refers to the inability of older adults to inhibit irrelevant information resulting in lower performance on a working memory task but enhanced performance when the previously irrelevant information is subsequently tested (e.g. Campbell et al. 2010). However, in our design we do not expect this to have a large influence. Even though location was not relevant during the 2-back task, the information was not conflicting and could even be used as a cue as a target could only be in the same location as two trials previously. Secondly, hyper-binding only occurs under fully implicit instructions (Campbell and Hasher 2018). In our task, participants are made explicitly aware of the link between the tasks. Campbell and Hasher (2018) showed that the effect of hyper-binding in older adults disappears when made aware of the connection between the tasks. Finally, our previous study in which we studied the effect of age on memory with this task design, did not show an advantage for older adults on the subsequent memory task (for a more extensive discussion on the task design see Lugtmeijer et al. 2019). A third difference is in task encoding, the subsequent memory task is unexpected. While encoding for working memory is typically shallow and based on rehearsal, encoding for a planned long-term retention task is more elaborative, which is beneficial for episodic memory but less essential for working memory (Cowan 2019; Craik & Watkins, 1973). While this might result in associations with different neural substrates than typically found in explicit episodic memory tasks, these instructions ensure that the encoding strategy is not different between the tasks. Therefore, this design is more sensitive to detecting possible overlapping substrates for working memory and episodic memory.

For clinical cognitive assessment it is relevant to take into account that stroke patients might have an altered response bias, especially because our results show that stroke can affect response bias towards a more liberal and a more conservative bias.

In conclusion, stroke can result in both working memory and episodic memory deficits. This study indicates that discriminability in working memory and episodic memory are two distinct processes. LSM analyses suggested there might be independent regions that are associated with working memory and episodic

memory performance. These findings largely support the multicomponent view of memory.

## Supplementary materials

**S1.** List of number of subjects with a lesion per ROI.

# Chapter 4

Feature recall and binding in
visual working memory in stroke patients

## Abstract

Visual memory for objects involves the integration, or binding, of individual features into a coherent representation. We used a novel approach to assess feature binding, using a delayed-reproduction task in combination with computational modeling and lesion analysis. We assessed stroke patients and neurotypical controls on a visual working memory task in which spatial arrays of colored disks were presented. After a brief delay, participants either had to report the color of one disk cued by its location or the location of one disk cued by its color. Our results demonstrate that, in the controls, report imprecision and swap errors (non-target reports) can be explained by a single source of variability. Stroke patients showed an overall decrease in memory precision for both color and location, with only limited evidence for deviations from the predicted relationship between report precision and swap errors. These deviations were primarily deficits in reporting items rather than selecting items based on the cue. Atlas-based lesion-symptom mapping showed that selection and reporting deficits, precision in reporting color, and precision in reporting location were associated with different lesion profiles. Deficits in binding are associated with lesions in the left somatosensory cortex, deficits in the precision of reporting color with bilateral fronto-parietal regions, and no anatomical substrates were identified for precision in reporting location. Our results converge with previous reports that working memory representations are widely distributed in the brain and can be found across sensory, parietal, temporal, and prefrontal cortices. Stroke patients demonstrate mostly subtle impairments in visual working memory, perhaps because representations from different areas in the brain can partly compensate for impaired encoding in lesioned areas. These findings contribute to understanding of the relation between memorizing features and their bound representations.

## Introduction

Visual deficits are common following stroke and vary widely, from reduced acuity and visual field loss, to visual inattention and deficits in perceiving specific features (Beaudoin et al., 2013; Rowe et al., 2017). Visual perception is also the basis for visual working memory, the retention of visually perceived features and objects over a short period of time that is required for many everyday tasks and important for subsequent episodic memory formation. In this study, we investigated whether stroke affects visual working memory while perception is spared. Moreover, we examined whether stroke can result in specific impairments of feature binding in working memory, that is, the ability to memorize which visual features belong to the same object.

Various previous studies have investigated the effects of ageing and neurological conditions on feature binding in working memory. While some early work suggested that binding memory is selectively impaired in healthy ageing (Cowan et al., 2006; Mitchell et al., 2000), several more recent studies have consistently concluded that there is a general decline of working memory performance in older adults, but no specific impairment for feature binding (Brockmole et al., 2008; Pertzov et al., 2015; Rhodes et al., 2016). In contrast, there is strong evidence that binding memory, compared to individual features, is selectively impaired in Alzheimer's disease (Liang et al., 2016; Parra et al., 2009) and in patients with temporal lobe damage following a form of autoimmune encephalitis (Pertzov et al., 2013), but to date no studies have investigated whether stroke patients show similar impairments. Stroke may result in focal lesions on the one hand, but on the other hand also in wide-spread disruptions of network activation (Adhikari et al., 2017). Consequently, it is hypothesized that in addition to stroke patients as a group differing from stroke-free controls in terms of working memory performance, specific impairments may occur due to a lesion in a key region. Lesion-behavior mapping was used to identify these regions.

To evaluate working memory performance in stroke patients and healthy controls, we use a delayed reproduction task, in which participants are briefly presented with a visual array of sample stimuli and then are instructed to report a feature (e.g. color, location) of a cued item on a continuous scale (Wilken and Ma, 2004). This type of task provides a sensitive measure of recall precision, and in addition allows us to detect deficits in memory for feature binding. This could be reflected by an increase in swap errors (Bays et al., 2009; Pertzov et al., 2015), in which participants correctly report a feature that was present in the sample array, but does not belong to the cued target item.

Two recent computational models have proposed that a key cause of swap errors is imprecision in memory for the cue feature (Oberauer and Lin, 2017; Schneegans and Bays, 2017). In the neural population model of Schneegans and

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Bays, the features of each item are represented jointly in a conjunctive population code. Noise in neural activity causes errors in retrieving memorized features. This model explains the observation that swap errors occur more frequently if memory for the cue feature is less precise (e.g. using color cues instead of location cues; Rajsic and Wilson, 2014), and that swap errors are more likely across items that are similar in their cue feature (Bays, 2016; Emrich and Ferber, 2012; Rerko *et al.*, 2014).

To detect possible deficits in binding memory in visual working memory, we combined two variants of a delayed reproduction task that differ with respect to the visual feature – color or location – that is used as cue, and the feature that has to be reported. By fitting the results with the neural population model, we obtain both estimates of the memory precision when reporting each feature, and of the proportion of swap errors when each feature is used as a cue. In cognitively unimpaired adults, it has been shown that a single conjunctive memory representation can explain performance in both tasks variants (Schneegans and Bays, 2017). If there is a specific impairment of binding memory in stroke patients, we expect to see specific deviations from this pattern.

## Materials and Methods

### Participants
Eighty-eight patients from the Functional Architecture of the Brain for Vision (FAB4V) study, a multi-centre prospective cohort study on vision and cognition after ischemic stroke in adults, participated in this study. The Medical Review Ethics Committee Utrecht approved the study (30-06-2015), and written informed consent according to the Declaration of Helsinki, was obtained from all participants prior to participation. Exclusion criteria were: haemorrhagic stroke, cerebral venous sinus thrombosis, pre-existing cognitive decline (score ≥ 3.6 on the IQCODE Dutch version; Schmand *et al.*, 1997) or dementia, psychiatric disorder, severe aphasia, pre-existing visual impairment, and disrupted perception as a consequence of stroke, like hemianopsia. Cognitive measurements took place between April 2016 and March 2020. Patients were at least 4 weeks post-stroke, 46 patients were assessed on visual working memory in the subacute stage within 6 months, 42 in the chronic stage between 6 months and 3 years after stroke (range in days 29 – 1,055, median 106 days). All patients underwent an MRI scan within 6 months post-stroke (range in days 17 – 186, median 52 days). Based on the Bells test (Gauthier *et al.*, 1989) none of the patients had neglect. Five patients were excluded from analyses because of missing data due to technical or logistic reasons (*N* = 3) and fatigue (*N* = 2), resulting in a total sample size of 83 patients (*M*age (*SD*) = 63 (11); m:f = 61:22; *M*education [range] = 5.3 [2-7]).

A stroke-free control group (*N* = 88), matched for age, was recruited, without a history of neurological disease or cognitive decline (self-report). Thirteen controls were excluded because of incomplete data (all due to technical or logistic reasons) resulting in a control group of 75 subjects (*M*age (*SD*) = 60 (11); m:f = 38:37; *M*education [range] = 5.9 [4-7]). Controls were recruited via social networks or were spouses or family members of patients.

All participants had normal or corrected-to-normal visual acuity, and none reported color blindness.

### Paradigm
Participants performed a delayed reproduction task that assesses memory precision for color and location and for binding between those features (adapted from Schneegans and Bays, 2017, experiment 1). In one condition a location cue was given and participants were instructed to report the corresponding color, in the other condition a color cue was given and the location needed to be reported (Fig. 1). At the beginning of each trial a white fixation cross (diameter 0.75° of visual angle) was presented for 2 s. This was followed by a sample array showing three colored discs (0.5° radius) positioned on an imaginary circle (6° radius), cantered on the fixation cross. Locations were randomly selected for every trial with a minimum distance of 30° to neighbours. Colors were chosen at random from a color wheel, defined as a circle in Commission Internationale de l'Eclairage (CIE) L*a*b* coordinates with constant luminance (L* = 50), centre at a* = b* = 20, and radius 60. Colors for the different discs were separated at least 30° on the color wheel. After a presentation duration of 2 s, a black display with fixation cross was presented for 1 s followed by a cue. One of the three discs from the sample array was selected as the target. In the *report-color* condition, a white disc (0.25° radius) appeared at the location of the target item. Participants adjusted the color of a centrally presented disc (0.75° radius) by cycling through the color wheel until the color matched the recalled color of the target. In the *report-location* condition, the cue was a centrally presented disc that matched the color of the target. Participants adjusted the location of a white disc (0.25° radius) on the imaginary circle to match the target's recalled location. Participants responded using an input dial (PowerMate USB Multimedia Controller, Griffin Technology) and were instructed to answer precisely rather than fast. Participant performed one block of 40 trials per task condition, each preceded by six single item practice trials. The order of the blocks was counterbalanced across participants.
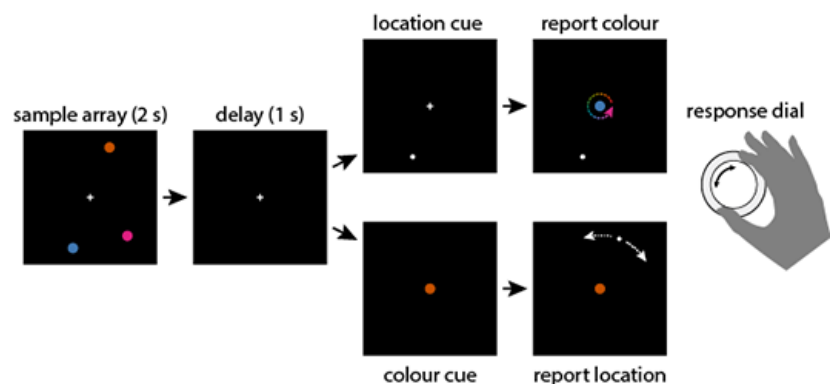
Fig. 1. Delayed reproduction task with two conditions. The sample array consists of three disks with randomly chosen colors and locations on an imaginary circle around the fixation point. In the report-color condition a location is cued and participants use a response dial to report the matching color. In the report-location condition a color cue is given and participants use the dial to adjust a small white disk to the matching location.

## Behavioral data processing

Stimulus locations and colors were analysed and are reported with respect to the circular feature space of possible values, -π to π radians. Recall error was calculated as the distance in radians between the reported value and the true feature value of the target item. Deviation between the response and feature values of non-target items in each trial was calculated to assess evidence for swap errors (erroneous report of the feature of a non-target item). Histogram plots of non-target deviations were corrected for the effects of minimum feature distance between items within a trial (Schneegans and Bays, 2017; see SI for details).

## Neural binding model

The neural binding model (Schneegans and Bays, 2017) extends a neural population model of working memory (Bays, 2014) to explain patterns of swap errors in delayed reproduction tasks. It assumes that the features of all sample items are encoded in the spiking activity of an idealized population of neurons with conjunctive coding (Fig. 2A). Each neuron's mean activity is determined by its tuning functions for both stimulus color and stimulus location, modelled as von Mises distributions with different concentrations for the two features.

Spiking activity for each neuron is generated by an independent Poisson process.
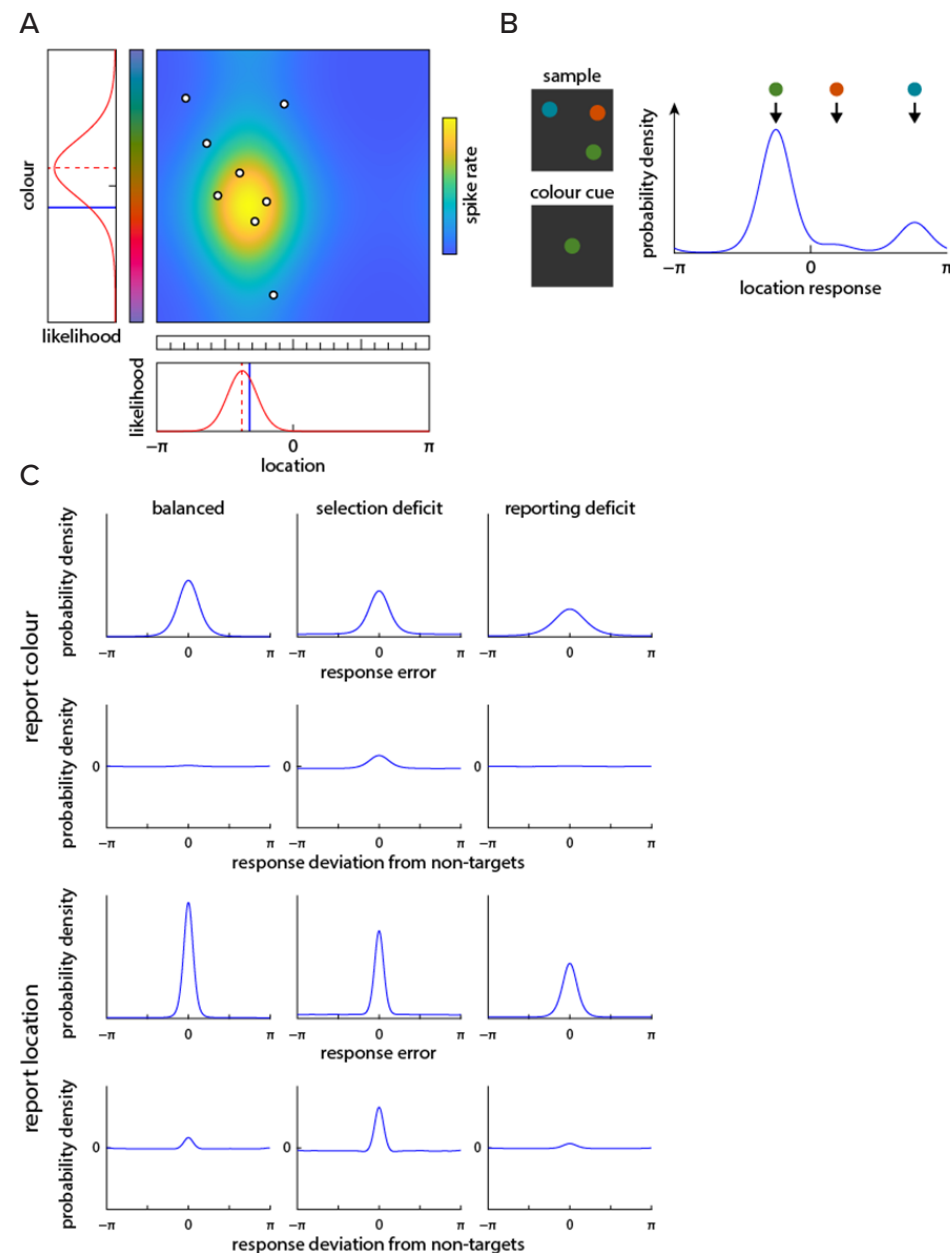


Fig. 2. Neural binding model. (A) The features of a sample stimulus (blue lines) are encoded in the spiking activity of a neural population with conjunctive coding (white dots illustrating preferred stimulus values associated with spikes in an example trial). Maximum likelihood

decoding from the spiking activity yields noisy estimates of the true values (red dashed lines). (**B**) The model predicts a response probability distribution for each trial, with decoding variability in the report feature leading to imprecision in responses, and decoding variability in the cue feature dimension leading to swap errors depending on cue similarity. (**C**) Model predictions for distributions of response errors are obtained by averaging response probability distributions over many trials, aligned to the target or non-target report feature values. Effects of the binding index are shown for a model with other parameters held fixed at typical values for this task. Left column, the model with no deficit shows broad response error distribution with almost no swap errors in the color report, and a sharper distribution with some swap errors (indicated by the central peak in the distribution of response deviations from non-targets) in the location report. A selection deficit (middle column) increases the proportion of swap errors in both feature dimensions, which leads to longer tails in the response error distribution without affecting the shape of the central peak. A reporting deficit (right column) produces broader distribution of response errors, but does not affect the proportion of swap errors.

When a cue is presented in the delayed reproduction task, the feature values of all sample items are decoded from the noisy spiking activity by maximum likelihood estimation. The item whose decoded cue feature value is closest to the given cue is selected, and its decoded report feature value is generated as a response. Variability in decoding leads both to imprecision in the reported value and to swap errors (Fig. 2B), which occur when the decoded cue feature value of a non-target item is closer to the given cue than the decoded cue feature value of the actual target (see S1 for full model description and derivation of response distributions).

The model has three free parameters, namely the tuning curve widths for color and location, and a gain parameter determining the mean spike rate. We obtained separate model fits for each participant's data in the two task conditions, as well as a combined fit across task conditions for each participant. In the latter fit, the same conjunctive neural population underlies both color and location report, the only difference being which feature is used as cue and which is reported. This model makes predictions about the relationship between error distributions in the two tasks. Concretely, the pattern of reporting errors in one condition can be used to predict the pattern of swap errors in the other condition, dependent on the similarity of cue features between the target item and individual non-targets in each trial.

### Extended neural binding model

We extended the neural binding model to detect specific deviations from the predicted relationship between report precision and swap errors. We allow for the possibility that only a certain proportion of all available spikes contribute to the selection of the presumed target item (with others only contributing to the decoding of the report feature value), leading to a selective impairment in selecting the target item based on the given cue. We also allow for the converse effect, in which all spikes contribute to the selection of the cued item, but only a subset can be used in decoding the report feature value, resulting in a selective decrease in report precision. These adjustments are parameterized with a new free parameter in the model, the *binding index* (Fig. 2C). With a binding index of zero, the model behaves exactly like the original neural binding model. An index of -1 indicates maximum selection deficit (the selection of the cued item is completely random), and a value of 1 indicates maximum reporting deficit (the response distribution is always uniform).

In addition to this binding index, we derive measures of memory precision for color and location from the model fits of each participant. We use as precision measure the circular standard deviation of the decoding error for each feature, computed from the fitted model but excluding the adjustment of available spikes based on the binding index (and therefore independent of any selection or reporting deficits reflected in that parameter).

### Statistical analysis

Hypothesis testing was conducted using t-tests. Models were compared using the Akaike information criterion with correction for small sample size (AICc), computed for each participant based on the maximum likelihood fit of each model (see S1 for details).

### Neuroimaging

Participants underwent a 3-T MRI scan, at the Radboudumc and UMCG on the Siemens Magnetom Prisma, at the Amsterdam UMC and UMCU on the Philips R5. For the Siemens scanners, sequence details were as follows: T2 FLAIR (TI = 1650ms, TR = 4800ms, TE = 484ms, [FOV] = 280mm, voxel size 0.9×0.9×0.9mm3). For the Philips scanners, sequence details were: T2 FLAIR (TI = 1650ms, TR = 4800ms, TE = 253ms, [FOV] = 250mm, voxel size 1.12×1.12×0.56mm3).

Lesions were manually delineated using ITK-SNAP software (Yushkevich et al., 2006). The FLAIR and binary lesion mask were normalized to an older adult MNI template using the plug-in clinical toolbox for SPM (Crinion *et al.*, 2007; Rorden *et al.*, 2012).

### Lesion analyses

For the associations between lesion location and outcome measures we used the three performance measures obtained from the extended neural binding model fits: binding index, memory precision for color, and memory precision for location (circular standard deviation of the decoding error).

Atlas-based LSM (lesion-symptom mapping) was used to investigate which lesions are associated with a reporting or selecting deficit, and with memory precision. For the binding index the association with lesion location was tested two-sided. For memory precision, associations were tested one-sided, with higher behavioral scores indicating worse performance. Statistical lesion analysis software NiiStat was used (https://github.com/neurolabusc/NiiStat). Atlas-based analysis is based on the cumulative lesion burden in a specific ROI (region of interest), instead of investigating lesions on a voxel-wise basis. The advantage is effectively increasing the number of areas that have sufficient coverage across participants. The assumption is that lesions in the same ROI affect behavior in the same way. In addition, a ROI-based approach reduces the strict control needed for multiple testing that is required in voxel-wise analyses. Cortical ROIs are based on Brodmann areas (BA). For white-matter ROIs the CAT atlas was used (Catani and De Schotten, 2008); https://www.natbrainlab.co.uk/). Only ROIs with a lesion coverage of at least 4 (6%) subjects were included. To correct for multiple comparisons permutation testing was set to 5,000 permutations at $p < .025$ for the binding index (two-sided) and at $p < .05$ for reporting precision (one-sided). Lesion volume, age, education, gender, and interval between MRI and assessment were included as covariates and were regressed on both behavioral and lesion data (DeMarco and Turkeltaub, 2018).

## Results

To investigate visual working memory after stroke, we assessed stroke patients and age-matched controls in two delayed-reproduction tasks. Participants viewed a sample array of colored disks, and after a brief delay either had to report the color of one disk cued by its location (report-color condition) or the location of one disk cued by its color (report-location condition). We fitted a neural population model to the behavioral data to detect specific deficits either in memory for feature bindings or in the ability to report memorized features. Second, we investigated which lesion locations were associated with recall precision and with deficits in reporting or selecting features.

### Behavioral data

The behavioral data are shown in Fig. 3. Consistent with previous studies, the distribution of response errors is broader overall in the report-color (Fig. 3A) than in the report-location condition (Fig. 3D). Nonetheless, the error distribution for location reports shows long tails, with above-zero proportion of responses even at the largest deviations from the target location. This is consistent with the
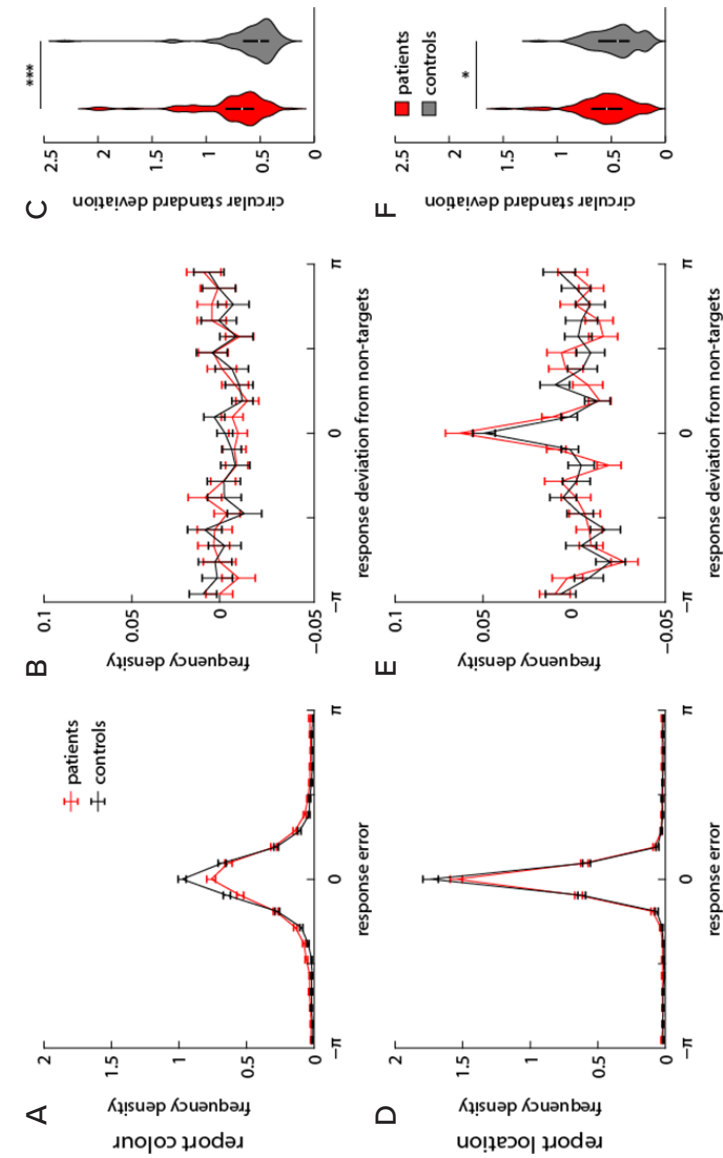


**Fig. 3.** Behavioral data. Data for the report-color condition (**A-C**) and the report-location condition (**D-F**). From left to right: histogram of response errors, histogram of response deviations from report feature values of non-targets in each trial, and distribution of response precision (as circular standard deviation, higher values indicating less precise) in each participant group. Violin plots show the median (white dot), interquartile range (black line), and kernel density plot (Gaussian kernel with bandwidth of 0.05).

presence of swap errors, in which participants incorrectly report the location of a sample item that is not the cued target.

The occurrence of such swap errors can be detected by plotting the histogram of response deviations from the report feature values of all non-target items in each trial (Fig. 3B and E). In the absence of swap errors, these distributions should be uniform (after correcting for effects of minimum distance between items' feature values). However, in the report-location condition (Fig. 3E) we observed a significant central tendency that indicates a clustering of responses around the locations of non-target items and thus the occurrence of swap errors (mean absolute deviation from target features: patients *M (SD)* = 1.74 (0.10) vs chance 1.78 (0.07), $t(82)$ = 5.82, $p$ < .001, controls 1.77 (0.10) vs chance 1.80 (0.07), $t(74)$ = 4.05, $p$ < .001). In the report-color condition the central peak is absent, and we instead find a small, but significant tendency to avoid the colors of non-target items (Fig. 3B; mean absolute deviation: patients 1.77 (0.12) vs chance 1.75 (0.08), $t(82)$ = 3.18, $p$ = .002, controls 1.79 (0.09) vs chance 1.77 ( 0.07), $t(74)$ = 2.99, $p$ = .004).

Despite the overall similarity in response distributions between the two participant groups, we find that recall performance is impaired in stroke patients (Fig. 3C and F). An independent-sample t-test shows that the circular standard deviation as a measure of variability is higher (indicating lower precision) in both conditions for patients compared to controls (report-color: patients *M (SD)* = .76 (.35); controls *M (SD)* = .58 (.28); $t(156)$ = 3.60, $p$ < .001; report-location: patients *M (SD)* = .56 (.25); controls *M (SD)* = .47 (.21); $t(156)$ = 2.45, $p$ = .02).

## Model fits

We fitted the single-trial data of participants with a neural population model that has previously proved successful in capturing performance on similar tasks (Schneegans and Bays, 2017). The model assumes that the location and color of each item are encoded together in a conjunctive population code, such that each spike from this population yields a sample of both features of an item. Variability in decoding the memorized feature values from noisy spiking activity is used to explain both imprecision in reporting a target feature and the occurrence of swap errors, which is due to uncertainty in selecting an item based on the given cue.

We found that, for the majority of participants, performance in both conditions is well explained by a single conjunctive population code, varying only in which feature is used as a cue and which is to be reported. This combined model provided a better quality of fit than separate neural binding models fitted to each task condition independently, as measured by AICc scores (patients: combined better than separate fit for 68 out of 83, mean ΔAICc = 1.71; controls: 67 out of 75, mean ΔAICc = 2.82). This supports the hypothesis that a single source of recall variability for each feature can explain both report imprecision and swap errors in the two task conditions.

Because stroke is a heterogeneous syndrome, we wanted to be able to quantify specific memory deficits in individual stroke patients. We therefore relaxed the neural binding model's assumption that there is a fixed relationship between report precision in one task condition and frequency of swap errors in the other condition. We introduce a binding index as a new parameter that can capture specific impairments either in selecting a cued item or in reporting the feature of an item once it is selected, by controlling what proportion of spikes contributes to item selection and report feature decoding, respectively. This binding index can take values between -1 (maximum selection deficit) and 1 (maximum reporting deficit).

Fig. 4 shows fits of both the original neural binding model (blue) and the extended model (red) to the response distributions of selected patients illustrating different forms of recall deficits. Model fits for participants in Fig. 4A and B produce values of the binding index close to zero, indicating neither selection nor reporting deficits, and consequently show near identical fits of the two models. Note that these participants still differ substantially in their memory precision for both color and location, but in both cases the frequency of swap errors is consistent with the report precisions. In contrast, the individuals in Fig. 4C and D show specific selection deficits, which suggests that memory for the binding between cue and report feature is impaired: the frequency of swap errors is higher than would be expected based on the participant's reporting precision in each feature. The original binding model in these cases fails to fully capture the observed proportion of swap errors, since it is constrained by the reporting precision. Finally, participants in Fig. 4E and F show evidence for specific reporting deficits. Both of these patients were able to use a color cue to reliably select the target item for the location report (indicating that they held the colors and their binding to locations in memory), but performed very poorly when reporting colors. In these cases, the model without binding index is forced to overestimates the frequency of swap errors in the report-location condition in order to better capture the very broad error distribution in the color report. (In the case of Fig. 4F, the extended model still overestimates the proportion of spatial swaps to a lesser degree, since it is still constrained by the assumption that reporting deficits are symmetrical between the two conditions.)

Model comparison using AICc scores showed that a non-zero binding index was preferred only for a small number of participants (patients: 12 out of 83, mean ΔAICc = 1.16 in favor of the original model; controls: 7 out of 75, mean ΔAICc = 1.41 in favor of the original model). This is expected if only a few participants show selective impairments of binding in visual working memory.

Figure 5 shows the distribution of performance measures derived from the model fits for patients and controls, namely estimates of memory precision for each feature dimension and binding index. Independent sample t-tests show that
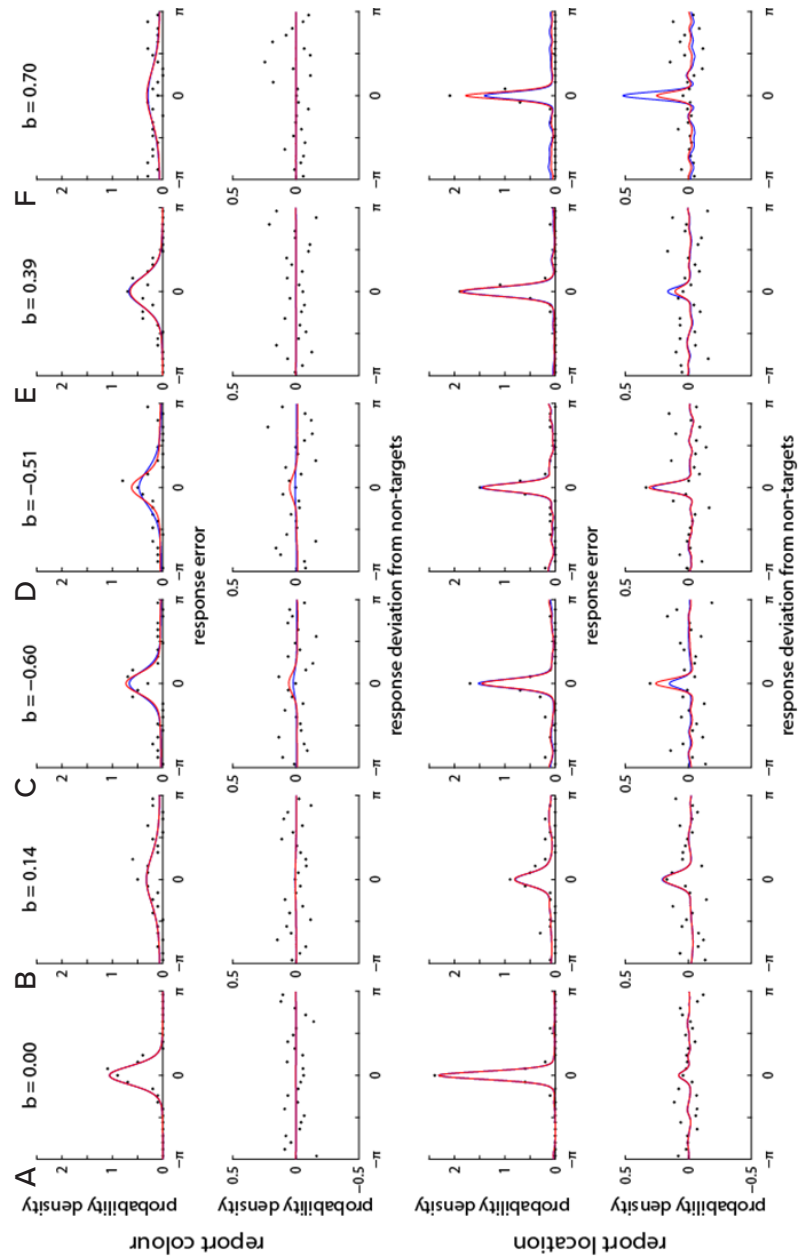
**Fig. 4.** Fits of neural binding model to behavioral data of individual patients. Response histograms of patients are shown as black dots, fits of the original neural binding model in blue and fits of the extended model in red. (**A, B**) Patients without selection or reporting deficit. The binding index is close to 0 so the model fits are near-identical. (**C, D**) Patients with binding deficit. The binding index is negative and the extended model fit indicates more binding errors than the original model fit. (**E, F**) Patients with reporting deficit. The binding index is positive and the extended model fit indicates less binding errors than the original model fit.
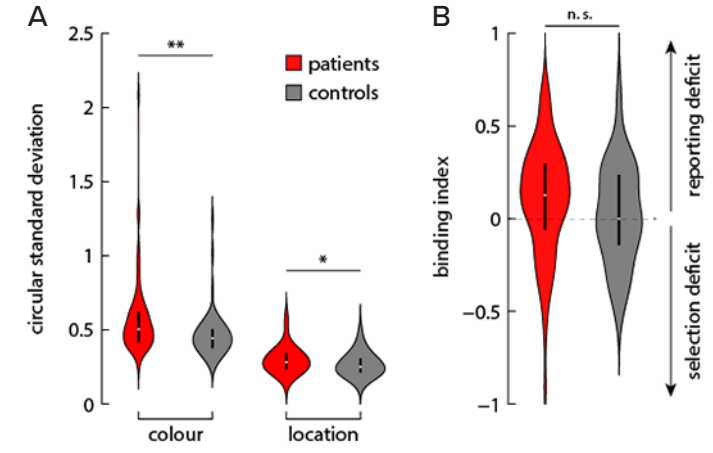


**Fig. 5.** Model based performance measures. Measures are based on maximum likelihood fits of the neural binding model to behavioral data of patients and controls. (**A**) Memory precision in each feature dimension. (**B**) Binding index, with negative values indicating a reporting deficit and positive values a binding deficit. Violin plots as in Fig. 3, with bandwidth of 0.05 for circular standard deviation and 0.1 for binding index.

patients have a significantly lower memory precision for both color and location compared to controls (color: patients $M (SD)$ = .57 (.26); controls $M (SD)$ = .46 (.15); $t(156)$ = 3.28, $p$ = .0013; location: patients $M (SD)$ = .30 (.09); controls $M (SD)$ = .27 (.08); $t(156)$ = 2.18, $p$ = .031).

The difference in binding index between patients and controls did not reach significance at the group level (patients $M (SD)$ = .11 (.30); controls $M (SD)$ = .02 (.27)); $t(156)$ = -1.80, $p$ = .07). Based on visual inspection of the results, we tested post hoc whether group means deviate from 0. The estimates of the binding index were significantly shifted towards the positive range in patients, indicating an overall tendency towards reporting deficits (single sample t-test, $t(82)$ = 3.25, $p$ = 0.002). In contrast, estimated binding indices were not significantly different from zero in controls ($t(74)$ = 0.79, $p$ = 0.44). Moreover, if we consider only participants in which the introduction of the binding index improves quality of fits, a majority showed a reporting deficit (positive binding index for 10 out of 12 patients and 4 out of 7 controls), indicating that specific deficits in feature selection are relatively rare.

We note that despite the overall tendency towards a reporting deficit, patients still showed a higher estimated proportion of swap errors when reporting location (patients $M (SD)$ = .05 (.05); controls .04 (.04); $t(156)$ = 2.76, $p$ = .04), due to the overall lower memory precision. In the color report, the difference in swap

frequency was not significant (patients $M (SD)$ = .02 (.04); controls $M (SD)$ = .01 (.02); $t$(156) = 3.73, $p$ = .09).

## Lesion analyses

Of the total sample of 83 patients 65 were included in these analyses. Eight were excluded because of a missing structural MRI scan, seven had no clear lesion on the MRI scan, three patients had widespread white matter hyperintensities. Median lesion volume was 3.06 cm3 (range .02 – 85.12 cm3). Lesions in the left hemisphere were most common ($N$ = 28), followed by lesions in the right hemisphere ($N$ = 21), bilateral lesions ($N$ = 13) and brain stem lesions ($N$ = 3). Figure 6 shows the lesion prevalence map.
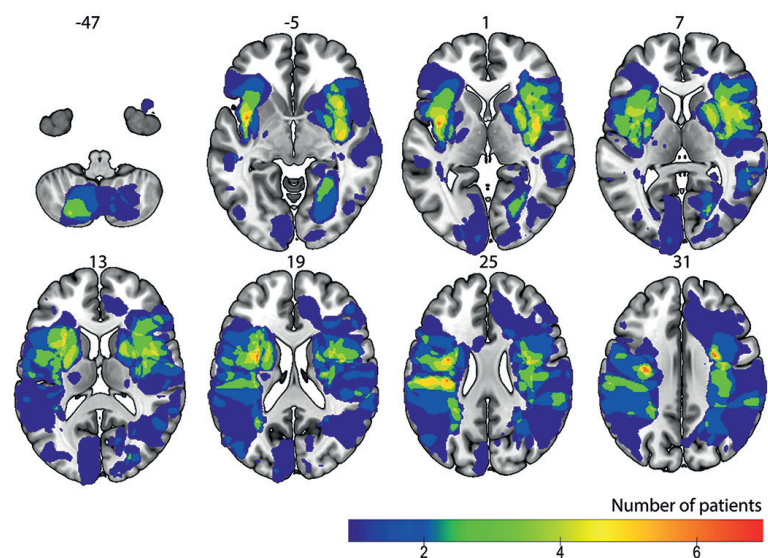


**Fig. 6.** Lesion density plot. Maximum overlap 7. MNI coordinates are specified for each axial slice. Left hemisphere is depicted on the left.

## Atlas-based lesion-symptom mapping

Of 82 cortical ROIs included in the Brodmann atlas, 37 (22 right hemisphere) were covered by at least 4 lesions. Twenty-seven white-matter tracts of 32 defined in the CAT atlas had sufficient lesion coverage (see S2 for details). Behavioral variables of interest were binding index, and precision of reporting color and reporting location indicated by the circular standard deviation. Lesion volume, age, education, gender, and interval between MRI and assessment, were included

as covariates. Covariates were corrected for by regressing them on the behavioral and lesion data.

Lesion status in BA3, the primary somatosensory cortex, in left hemisphere was negatively associated with the binding index, indicating selection deficits (threshold $z$ < -3.42 and $z$ > 2.86, $z$ = -3.56). Precision in the report-color condition was associated with BA6, premotor and supplementary motor cortex, in the right hemisphere (threshold $z$ > 4.55, $z$ = 4.65), and with BA44, Broca's area, also in the right hemisphere (threshold $z$ > 4.55, $z$ = 5.25). In the left hemisphere precision in reporting color was associated with BA7, superior parietal lobe, in the left hemisphere (threshold $z$ > 4.55, $z$ = 5.19) and BA41, auditory cortex (threshold $z$ > 4.55, $z$ = 5.61), the posterior segment of the arcuate fasciculus (threshold $z$ > 4.32, $z$ = 5.77), and the optic radiation (threshold $z$ > 4.32, $z$ = 4.99). For precision in the report-location condition there were no significant neural correlates. Results are summarized in Table 1 and Fig. 7.

**Table 1.** Results from the atlas-based lesion symptom mapping analysis

| ROI (Fig 7.) | Description | $N$ subjects | Outcome measures |
|---|---|---|---|
| BA3 left (1) | Primary somatosensory cortex/ postcentral gyrus | 7 | - binding index |
| BA6 right (2) | Premotor and supplementary motor cortex | 11 | - precision color |
| BA7 left (3) | Visuo-motor coordination/ superior parietal lobe | 4 | - precision color |
| BA41 left (4) | auditory cortex | 5 | - precision color |
| BA44 right (5) | Broca's area/inferior frontal gyrus | 9 | - precision color |
| Posterior segment arcuate left (6) | Connecting the inferior parietal lobe to Wernicke's area | 6 | - precision color |
| Optic radiation left (7) | Connecting the lateral geniculate nucleus to the primary visual cortex | 13 | - precision color |
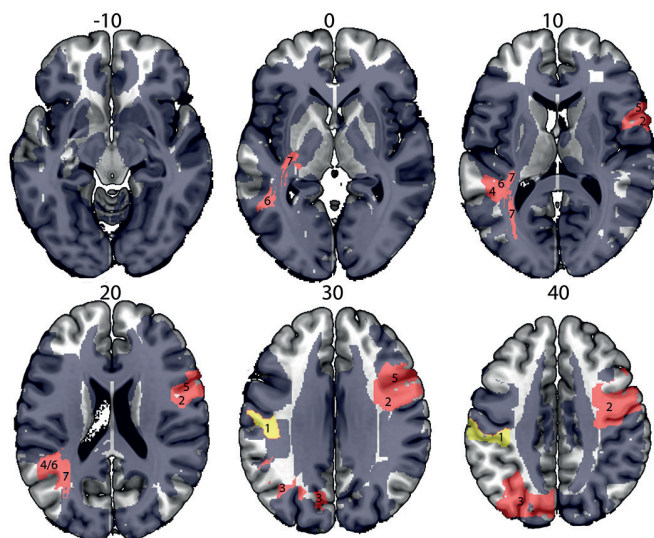
**Fig. 7**. Results of the atlas-based LSM analysis. Shaded areas show which regions are included in the analysis (≥ 4 overlapping lesions). ROIs significantly associated with the binding index are plotted in yellow; ROIs significantly associated with precision in reporting color in red. No areas were significantly associated with precision in reporting location. The numbers correspond to Table 1. Coordinates correspond to MNI standardized space. Left hemisphere is depicted on the left.

## Discussion

Mechanisms underlying the binding of visual features have been studied in cognitively unimpaired individuals, as well as in ageing and patient populations (for a review see Schneegans and Bays, 2019). In the current study we investigated feature recall and feature binding in visual working memory in stroke patients to assess if specific deficits in visual working memory in this population occur and if so, what the neuroanatomical basis is. Stroke patients showed an overall decrease in memory precision for both color and location, while binding deficits were rare. Visual representations were associated with a distributed network of brain regions.

We used a novel approach to assess deficits in feature binding, using two symmetrical conditions of a delayed reproduction task in combination with computational modeling and lesion analysis. We built on theoretical work and behavioral results in healthy adults suggesting that the same variability in memory retrieval can account for errors in reporting a feature and for swap errors when the

feature is used as a cue (Bays *et al.*, 2009; Oberauer and Lin, 2017; Schneegans and Bays, 2017). Previous studies have qualitatively controlled for the effect of memory imprecision in the cue feature (e.g., by having participants first select a shape that was present in the sample array before reporting its location; Pertzov *et al.*, 2015; Pertzov *et al.*, 2013). However, the design used here enables quantification of memory precision for a visual feature when it has to be reported and when it is used as cue, in order to determine whether an additional source of binding errors is needed to explain the behavioral results.

We fitted the behavioral data with an existing neural population model that assumes a single conjunctive memory representation supports binding and recall. We also extended this model by introducing a binding index that can capture and quantify specific deviations from the assumption of a single source of variability. The implementation of such deficits in the binding model is broadly compatible with models assuming mixed representations with only a subset of neurons contributing binding information (Bouchacourt and Buschman, 2019; Matthey *et al.*, 2015). However, given that lesion effects vary substantially between participants, we refrained here from trying to specify a concrete neural mechanism for observed impairments, and confined ourselves to quantifying the memory deficits as deviations from the existing model.

The behavioral results for the control group confirmed the assumption made in previous work that report imprecision and swap errors are explained by a single source of variability in healthy individuals. This was supported both by model comparison between the original and the extended binding model and parameter estimates for the binding index in the extended model. In patients, we found an overall decrease in memory precision for both color and location, but only limited evidence for deviations from the predicted relationship between report precision and swap errors. Critically, the deviations that we observed tended to be in the direction of a reporting deficit—patients tended to be worse at explicitly reporting a memorized feature value (especially for colors) than at using it as a cue to retrieve another feature of a matching item. This shows that selective impairments in memory for feature binding are rare for the patient group analysed here.

One could argue that the observed reporting deficits in patients are due to the response procedure, in particular in the report-color condition where participants had to adjust the color of a central probe stimulus via a response dial. This might induce stronger interference than e.g. selection from a color wheel with all response options visible simultaneously. Previous studies did not find any performance difference between the two response modes in healthy adults (Bae *et al.*, 2014), and here we found no consistent evidence for reporting failures in controls, but we cannot rule out that stroke patients may be particularly susceptible to certain forms of interference which may have influenced the results.

Results from our atlas-based LSM analyses showed distinct neural profiles. We identified one lesion location associated with specific binding deficits, multiple lesion locations associated with memory precision for color, and none for location memory precision. In our behavioral data the difference between patients and controls is also more pronounced in the report-color condition compared to the report-location condition.

Critical lesions for precision in color memory in the left hemisphere are the superior parietal lobe, auditory cortex and the posterior segment of the arcuate fasciculus and the optic radiation, and in the right hemisphere the premotor/ supplementary motor cortex and the inferior frontal gyrus. This pattern of a behavioral deficit as a consequence of damage to one of several brain structures is known as the equivalence brain mode and has been described in relation to memory deficits before (Godefroy *et al.*, 1998; Toba *et al.*, 2020). Both the right inferior frontal gyrus and supplementary motor area have previously been associated with visuospatial working memory (Baddeley, 2003; Teramoto, *et al.*, 2016; Xiang *et al.*, 2012), and with categorization (Adams and Janata, 2002; Lee *et al.*, 2013; Li *et al.*, 2020), for colors in particular (Liu *et al.*, 2019).

In all patients with a lesion in the auditory cortex in the left hemisphere, the lesion extended to the posterior segment of the arcuate fasciculus. As our task does not have an auditory component we focus on the posterior segment of the arcuate fasciculus. The posterior segment of the arcuate fasciculus in the left hemisphere is primarily associated with the language network, specifically lexical retrieval and feedback between visual and non-visual information (Nakajima *et al.*, 2019). Souza and Skóra (2017) showed that labelling of colors compared to articulatory suppression increased the quality of retention in visual working memory. A dual-content model has been proposed that distinguishes between a high-resolution channel that encodes color hues on a continuous scale, and a low-resolution channel that encodes the category of a stimulus (Bae *et al.*, 2015). Stroke patients with a lesion including the posterior segment of the arcuate fasciculus might be impaired on verbalizing color hues and as a consequence be less accurate in reporting color. Bae and colleagues (2015) suggested that categorization in visual working memory can take place at verbal and visual level. This view is in accordance with our LSM results that associated language related areas in the left hemisphere and medial and inferior frontal areas in the right hemisphere with precision of reporting color. Our stroke patients demonstrated mostly subtle impairments in visual working memory. Representations from different areas in the brain might in part compensate for impaired encoding in lesioned areas.

Previous studies associated the posterior parietal cortex with the binding of features in a change detection task for shape-color bindings (Birba *et al.*, 2017; Parra *et al.*, 2014) and with perceptual attention as measured by detection of

changes in color (Weber *et al.*, 2017). Results from our atlas-based LSM study identified the superior parietal lobe only for precision in the report-color condition. Binding deficits were rare in our study sample, which might explain why we did not detect an association for binding with this area.

An unexpected result was that a critical lesion location for specific binding deficits was found in the left primary somatosensory cortex (BA3). To our knowledge, to date only one study showed that visual working memory can be decoded from activity in somatosensory areas (Christophel and Haynes, 2014). This study made use of a similarity detection task for complex and colored motion stimuli. It has been suggested that representations in somatosensory areas are specific for complex dynamic stimuli (Christophel and Haynes, 2014). An alternative explanation is that the somatosensory cortex is anatomically located in the centre of the fronto-parietal functional connectivity network for visual working memory (Siegel *et al.*, 2016). Future studies should investigate the role of somatosensory areas in visual working memory.

Our LSM analysis showed an association between precision in reporting color and the left optic radiation (Párraga *et al.*, 2012). While damage to the optic radiation has been associated with visual field deficits (Yogarajah *et al.*, 2009), as far as we are aware there are no studies that associate the optic radiation with color perception or memory. All visual areas, V1-5 bilaterally, were included in our analyses but were not associated with precision in feature reporting. As most patients have unilateral lesions, the visual cortex of the intact hemisphere might compensate for possible visual deficits.

Our analysis of associations between lesion location and memory deficits is by definition limited by the lesion coverage in the tested patient population. Due to the vascularization of the brain, certain areas are unlikely to suffer a stroke (Sperber and Karnath, 2017), including some regions that have been associated with working memory. The medial temporal lobe has been implicated to play a role for selective binding deficits in Alzheimer's patients (Liang *et al.*, 2016; Parra *et al.*, 2009), with conflicting findings in other populations (see Schneegans and Bays, 2019 for a review), but this area is not typically affected by stroke (Snaphaan *et al.*, 2009). The dorsolateral prefrontal cortex (BA9/46) and inferior parietal lobe (BA39/40) have been reported as essential for visual working memory (Baddeley, 2003), but only areas 40 and 46 in the right hemisphere had sufficient lesion coverage to be included in the present study. A promising direction for future research is using the regions identified in the present study to identify networks underlying visual memory based on resting-state MRI in healthy subjects (Sperber and Dadashi, 2020).

To conclude, we have presented a model that explains behavioral errors in feature reporting and binding in both neurotypical controls and stroke patients. In

the control group, report imprecision and swap errors in the delayed reproduction task can be explained by a single source of variability. Patients showed an overall decrease in memory precision for both color and location, but we found only limited evidence for deviations from the predicted relationship between report precision and swap errors. Binding deficits, precision in reporting color, and precision in reporting location are associated with different lesion profiles. The results from our study converge with previous reports, based on neuroimaging and other techniques, that working memory representations are widely distributed in the brain and can be found across parietal, temporal, and prefrontal cortices.

## Supplementary materials

**S1.** Model specifications
**S2.** List of number of participants per ROI

# Chapter 5

## Reviewing post-stroke
## working memory dysfunction

## Abstract

*Objective:* This review investigates the severity and nature of post-stroke working memory deficits with reference to the multi-component model of working memory. *Methods:* We conducted a systematic search in Pubmed up to March 2019 with search terms for stroke and memory. Studies on adult stroke patients, that included a control group, and assessed working memory function, were selected. Effect sizes (Hedges' $g$) were extracted from 50 studies (in total 3,084 stroke patients) based on the sample size, mean and standard deviation of patients and controls. Performance of stroke patients was compared to healthy controls on low-load (i.e. capacity) and high-load (executively demanding) working memory tasks, grouped by modality (verbal, non-verbal). A separate analysis compared patients in the sub-acute and the chronic stage. Longitudinal studies and effects of lesion location were systematically reviewed.
*Results:* Stroke patients demonstrated significant deficits in working memory with a moderate effect size for both low-load (Hedges' $g$ =-.58 [-.82 to -.43]) and high-load (Hedges' $g$ =-.59 [-.73 to -.45]) tasks. The effect sizes were comparable for verbal and non-verbal material. Systematically reviewing the literature showed that working memory deficits remain prominent in the chronic stage of stroke. Lesions in a widespread fronto-parietal network are associated with working memory deficits.
*Conclusions:* Stroke patients show decrements of moderate magnitude in all subsystems of working memory. This review clearly demonstrates the global nature of the impairment in working memory post-stroke.

## Introduction

Stroke survivors may be challenged not only with physical disability, but also with cognitive consequences. Dysfunction in perception, executive functioning, abstract reasoning, episodic memory and/or language has been found to be present in 60–70% of stroke patients (Nys et al., 2007; De Haan, Nys, & Van Zandvoort, 2006). Post-stroke cognitive impairment has been associated with functional dependency (e.g. Saxena, Ng, Koh, Yong, & Fong, 2007) and poorer quality of life (e.g. Mellon et al., 2015). Whereas post-stroke dementia and episodic memory function after stroke have been abundantly studied and reviewed (see, for instance, reviews by Pendlebury & Rothwell, 2009, and Lim & Alexander, 2009, respectively), a comprehensive overview of working memory deficits as a consequence of stroke is lacking. This is striking, as working memory/updating is considered to be one of the key subdomains of executive function along with shifting and inhibition (see e.g. comprehensive reviews by Chan, Shum, Toulopoulou, & Chen, 2008 and Friedman & Myake, 2017). Deficits in this memory system may not only affect other executive functions, but also episodic memory formation and retrieval (Bergmann, Kiemeneij, Fernández, & Kessels, 2013). Furthermore, a recent prospective cohort study on cognitive function and long-term functional outcome after stroke at a young age (<50) showed that only decline in working memory predicted poor functional outcome 11 years after the stroke (Synhaeve et al., 2015).

Working memory is generally thought of as a multicomponent system involved in goal-directed behavior that involves retaining and manipulating information (Baddeley, Hitch, & Allen, 2018; Chai, Abd Hamid, & Abdullah, 2018). A prominent model is that of Baddeley and Hitch (1974, Baddeley 2000). The model describes four subcomponents: the phonological loop (based on vocalisation and rehearsal), visuospatial sketchpad (for visuo-spatial rehearsal), the central executive, and the episodic buffer (Baddeley, 2012). The limited capacities of the phonological loop and the visuospatial sketchpad are measured by tasks that require passive maintenance of verbal and visuo-spatial information respectively (often referred to as short-term memory). Frequently used tasks to assess short-term memory capacity are forward span tasks. The involvement of the central executive, which can be described as the attentional control system, is measured by working memory tasks that involve both maintenance and processing, for example backward span tasks. The episodic buffer is responsible for the binding of information in working memory, and linking working memory to perception and long-term memory (Baddeley, 2000). This buffer is difficult to assess by standardized and process-pure tasks (Nobre et al., 2013) and its exact nature and properties have also been under debate (Heil, Rösler, & Rolke, 2003).

5

One of the reasons why there is no clear understanding of post-stroke working memory deficits is the heterogeneity in patient populations studied with respect to lesion locations, timing of assessment and small sample sizes. A second reason is that most studies only assess one component of working memory. A recent study (Karimian, Asgari, Neshat Doost, Oreizi, & Najafi, 2018) that investigated short-term memory, working memory, and long-term memory in the verbal, visuo-spatial, and visual domains in 35 stroke patients reports memory impairment on all aspects assessed. Most pronounced were impairments in visual short-term and long-term memory. A study by Nys and colleagues (2007) including 168 stroke patients reported a slightly higher percentage of patients with verbal memory impairment compared to visual memory impairment (25.6% and 22% respectively). In turn, a study in 39 acute stroke patients (Roussel, Dujardin, Hénon, & Godefroy, 2012) that investigated whether impairment in working memory remains after controlling for short-term memory capacity indicated that working memory impairment is a consequence of reduced short-term memory capacity.

A potential moderator of post-stroke working memory performance might be the time that elapsed since stroke. There is no consensus in the literature on working memory function in the chronic stage of stroke. For example, Kant et al. (2014) reported differences between chronic stroke patients and controls on all three working memory tasks they included, while McDonnell, Bryan, Smith and Esterman (2011) did not find any differences between patients and controls. Yet another study (Andrade, Brucki, Bueno, & Siqueira Neto, 2012) reported only decreased working memory performance in patients who were classified as having post-stroke vascular dementia.

Although there is clear evidence that working memory is affected at least in the acute stage of stroke, a detailed analysis is lacking as to whether these deficits concern the different components and processing modes of the working memory system to a similar extent. Unravelling this in stroke patients is crucial as subsystems of working memory are essential for many other cognitive processes and may be closely related to functional outcome. The primary objective of this meta-analysis and systematic review is to quantify the severity of post-stroke working memory impairment by comparing patients to stroke-free controls. Specifically disentangling the effects for low-load working memory tasks (mainly addressing the passive limited capacity store) and more cognitively demanding high-load working memory tasks (involving executive processing). We will also systematically compare outcomes in the verbal and non-verbal domains, and in the sub-acute and chronic stages of stroke. A secondary objective is to identify possible associations between post-stroke working memory impairment and lesion location. As patient studies often have small samples and most studies do not include different aspects of working memory, quantitatively reviewing all

available studies on this topic will help to provide a more comprehensive picture of working memory deficits after stroke.

## Method

PRISMA guidelines were used for the reporting of this systematic review (checklist provided in Appendix A; Moher, Liberati, Tetzlaff, & Altman, 2009).

### Data Sources
Electronic database Pubmed was searched for relevant studies; last search was performed on 10-03-2019. The following search terms were used: *"stroke", "post-stroke", "cva", "cerebrovascular accident", "cerebral vascular accident", "brain infarct*", "cerebral infarct*", "brain lesion", "ischemic lesion", "cerebral ischemia", "tia", "transient ischemic attack"* AND *"memory disorders", "memory", "cognitive domain*"*. Reference lists of selected articles were searched for potential missed articles.

### Study Selection and Eligibility Criteria
A two-step approach was used to select articles. Firstly, titles and abstracts of all search results were screened for the following characteristics by one reviewer (S.L.): (1) original article published in English, (2) participants are adults (>18 years of age), (3) study concerning stroke and/or transient ischemic attack (TIA) patients, (4) sample size of at least 10 patients, as single-case studies or case series often concern rare cases whose behavior might not be representative for the larger stroke patient population (5) outcome measures or descriptives include at least one working memory task; in case the abstract only mentioned memory function in general, the article was selected for full-text evaluation, (6) studies that only included patients with (subjective) memory complaints were excluded.

Secondly, 543 full-text articles were obtained from the selected studies and were reviewed on the following inclusion criteria: (7) a stroke-free control group was included as comparison, (8) clinical stroke patients in the sample (9) working memory function measured with a formal test or clearly described experimental paradigm, (10) treatment studies are included when baseline measures are reported. When two or more publications referring to the same sample were available, we extracted data only from the publication presenting the most accurate estimate, either because of sample size or outcome assessment. Two authors (S.L. and N.A.L.) independently performed the second step of the selection process. A meeting was held in case of disagreement which in all cases led to consensus.

Studies that included TIA patients were included in the meta-analysis as post-TIA cognitive impairment is often reported. A systematic review by Van Rooij, Kessels, Richard, De Leeuw, and van Dijk (2016) including 13 studies with data from 1,318 TIA patients, concluded that mild cognitive impairment is present in over a third of the TIA patients. When a mixed etiology lesion population was tested, the study was only included if separate results for the stroke patients could be retrieved.

## Data Extraction and Synthesis

Performance on working memory tests as compared to a healthy control group were extracted, as were participant characteristics, specific in- and exclusion criteria, and timing of assessment. First, overall performance on working memory tests was compared between stroke patients and healthy controls. Second, performances on low-load and high-load tasks were compared with a distinction between verbal and non-verbal tasks. Tests were considered low-load if they rely on remembering a limited amount of information over a short time, such as forward digit or spatial span tasks. In the working memory model of Baddeley and Hitch (1974) this is based on the phonological loop for verbal information and the visuo-spatial sketchpad for non-verbal information. Tasks that were considered high-load required some form of manipulation or updating, such as backward span or sequencing tasks, based on the central executive of the model. Tasks in which the stimuli (either visually or auditory) were digits, words, sentences or stories were categorized as verbal in nature. Tests were nonverbal in nature if stimuli were pictures of objects, scenes, line drawings or abstract figures. Third, a sub-analysis was conducted to examine the effect of timing of assessment (i.e. duration post stroke). Assessment within the first three months after stroke was considered sub-acute. Assessment after three months was considered as chronic. Qualitative synthesis of study results was performed with attention to lesion location. Working memory performance was compared between studies with specific inclusion criteria based on lesion location or imaging analyses relating lesion location to working memory performance. Working memory performance was compared within studies that selected groups based on lesion location.

## Risk of Bias Assessment

Risk of bias assessment was performed with the Research Triangle Institute (RTI) item bank, a tool to evaluate the bias and quality of observational studies (Viswanathan & Berkman, 2012; Viswanathan, Berkman, Dryden, & Hartling, L., 2013). As suggested by the RTI developers, slight adjustments were made to match the designs of the included studies (Appendix B). Four items were dropped and items were reformulated to fit a case-control design. Ten items that assessed the selection bias, detection bias, attrition bias, selective outcome reporting and confounding were selected.

## Statistical analysis

For the meta-analysis, sample sizes, means and standard deviations from the working memory tests were extracted from the studies. If necessary, corresponding authors were contacted to obtain these statistics based on the raw data. Summary statistics (Hedges' $g$) were calculated based on sample sizes ($N$), means of patients and controls ($M$) and standard deviations ($SD$) with the following formula: $g$ = StdDiff × $J$. StdDiff was calculated using the following formula: ($M1$ - $M2$) / $SD_{pooled}$, with $SD_{pooled}$ = $\sqrt{(((N1-1) \times SD1^2 + (N2-1) \times SD2^2) / (N1 + N2 -2))}$. The correction factor for different sample sizes is $J$, that was calculated as: 1 - (3 / (4 × df - 1)), where df = $N1 + N2$ - 2. Pooled variance was calculated by: $\sqrt{(1/N1+1/N2)} \times SD_{pooled}$. In case more than one outcome measure was reported, the average ES was calculated for the overall analysis. By using the mean of different outcome measures to calculate the effect size of the study we assume a correlation of 1 between different measures. This is a conservative approach as the actual correlation is probably less than 1 and the variance is lower than what we assume. The alternative is treating every outcome measure as fully independent, assuming a correlation of 0, which results in under-estimation of variance of the summary effect size. The actual overall effect size might therefore be slightly higher than our estimate. For the mixed-effect analyses of the effect of load and modality it was necessary to assume independence of outcome measures. Effect sizes were interpreted according to Cohen's (1992) convention of small (.20), medium (.50), and large (.80) effects for positive and negative values. Performance of stroke patients is lower compared to controls if the effect size (ES) is negative. Bias due to small sample sizes was corrected for by including sample size as a weighting factor (Hedges & Olkin, 1985). Random-effects models were used because of heterogeneity in populations studied and in outcome measures. Additionally, the goal is to generalize the results beyond the observed studies (Borenstein, Hedges, Higgins, & Rothstein, 2011). Heterogeneity was checked for by the use of the chi-square homogeneity test (Q). The fail-safe $N$ was calculated for each study and a funnel plot was made (Rosenthal, 1991). The fail-safe $N$ must to be larger than (5 × $k$) + 10, where $k$ refers to the number of studies included in the meta-analysis (Clark-Carter, 2010). This measure gives an indication of how many studies with null-results should be unpublished due to publication bias to nullify the effect. All analyses were performed using Comprehensive Meta-Analysis version 2.0 (Engelwood, NJ, USA, 2005).

## Results

### Selection of articles

The literature search resulted in 4,318 articles after removal of duplicates. Seven additional studies where identified by manually checking of reference lists of selected papers. In total, 553 were selected for full text screening. Seventy-five articles published between 1992 and early 2019 were eligible for inclusion. The eventual meta-analysis includes data of 3,084 stroke patients from 50 studies. An additional 25 studies of which the necessary statistics could not be retrieved or studies with overlapping samples but with relevant subgroup analyses were included in the systematic review. Figure 1 shows the flowchart of the literature search. Table S1 (online supplemental materials) shows the details of the studies included, these are: sample size and specific inclusion criteria, stroke type, age, interval between stroke and assessment, inclusion of prior stroke patients, inclusion of patients with pre-existing dementia, task load, task, Hedges $g$, and variance, and number of effect sizes for each primary study.

### Description of study populations

Ischemic stroke was the inclusion criterion for 30.6% ($k$ = 23) of the studies. A quarter of the studies (24.0%, $k$ = 18) included both patients with haemorrhagic and ischemic stroke. Concerning studies that included TIA patients and minor stroke, 5.3% ($k$ = 4) included both stroke and TIA patients, 2.7% ($k$ = 2) reported on patients with minor stroke[1], and 2.7% ($k$ = 2) included only patients with transient ischemic attack (TIA). One study (1.3%, $k$ = 1) included only patients with haemorrhagic stroke. A third (33.3%, $k$ = 25) did not specify stroke type. A majority of the studies (61.3%, $k$ = 46) did not select patients based on stroke location. Some studies (14.7%, $k$ = 11) included only patients with subcortical lesions. Only one community-based study was fulfilled the inclusion criteria, all other studies were hospital- or rehabilitation center-based. Twenty percent ($k$ = 10) studies included in the meta-analysis reported only one working memory measure. The mean number of outcome measures per study was 3.56. The maximum number of outcome measures per study was 14. Comparisons between left and right hemisphere stroke were made in 16% of the studies ($k$ = 12). Few studies included patients with stroke in one specific hemisphere (left: 6.7%, $k$ = 5, right: 9.3%, $k$ = 7). A total of 50 authors were approached to obtain additional information and necessary statistics from tasks separately (42.0%, $k$ = 21), from stroke patients

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1   Li et al. (2019) defined minor stroke by a score of 5 or less on the National Institute of Health Stroke Scale at admission and a diagnosis of ischemic stroke confirmed by neuroimaging; Mansueti, De Frias, Bub, and Dixon (2008) based inclusion on self-reported mild stroke for which medical attention was received, in a community-based study.
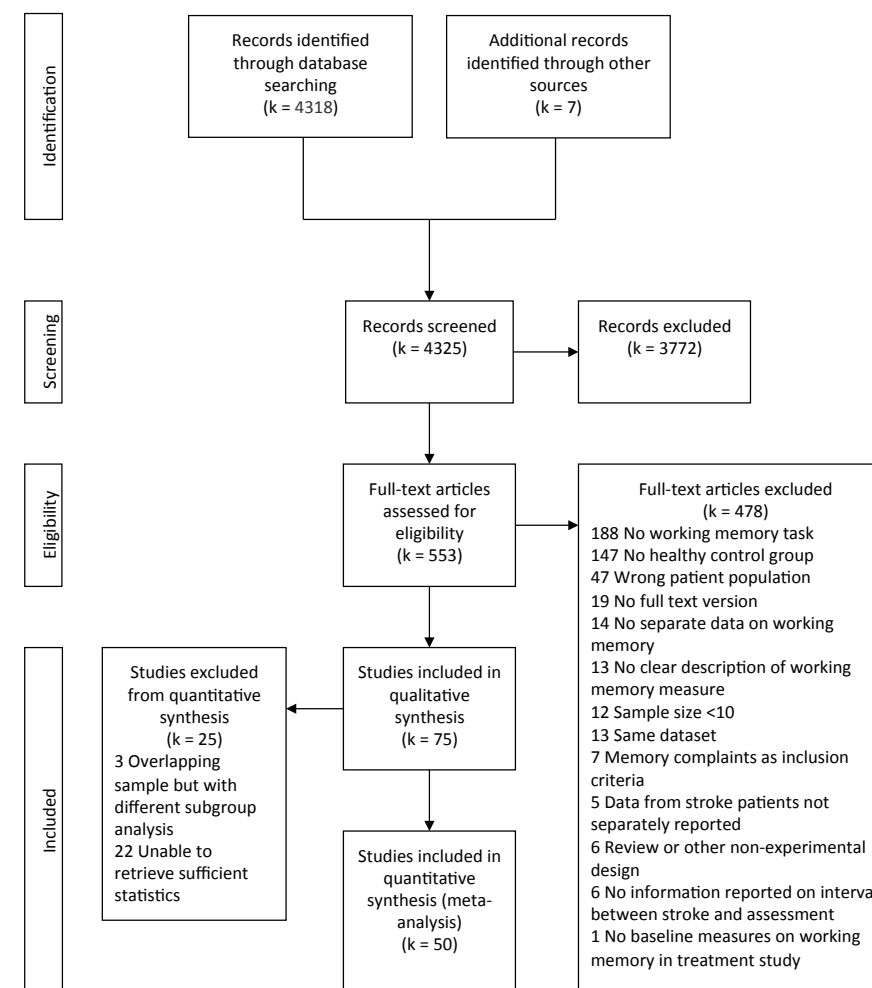


**Fig. 1.** PRISMA Flowchart

separately (12.0%, $k$ = 6), means and standard deviations that were not reported (32%, $k$ = 16), clarification on tasks or population (14%, $k$ = 7). This resulted in 16 studies that could be included in the meta-analysis. Of the 34 articles of which the authors did not respond, 22 were included in the qualitative analyses.

## Risk of bias assessment

Risk of bias assessment of individual studies based on the RTI items (see Appendix B and online supplemental materials Table S2) showed an unclear or high risk of confounding, as in more than two-third (72.0%, $k$ = 54) of the studies details on possible prior strokes or pre-existing dementia were not specified, and in almost half (56.7%, $k$ = 35) of the studies, in- and exclusion criteria for healthy controls were unclear. Although not invalidating the results of individual studies, it increased between-study heterogeneity. A majority of the studies (72.0%, $k$ = 54) did include an age and education matched healthy control group. A second source of hetero-geneity is the large variability in the intervals between stroke and assessment, both between and within studies. Almost all studies bear the risk of confirmation bias; only 5% of the studies ($k$ = 4) reported that assessors were blinded to the status of the participant (patient or control). As deficits are often prominent, it is unsurprising that other studies did not report assessors to be naive to the participants group. The funnel plot shows the relation between the sample size and the effect size (Fig. 2). The plot shows some asymmetry, which may partly be due to heterogeneity in outcome measures and partly be due to publication bias. Especially the lower right corner is empty, which indicates that there are no small studies with small effect sizes. The summary statistics of the meta-analysis as shown in Table 1 includes the *Fail-safe N* for each analysis as the number of studies
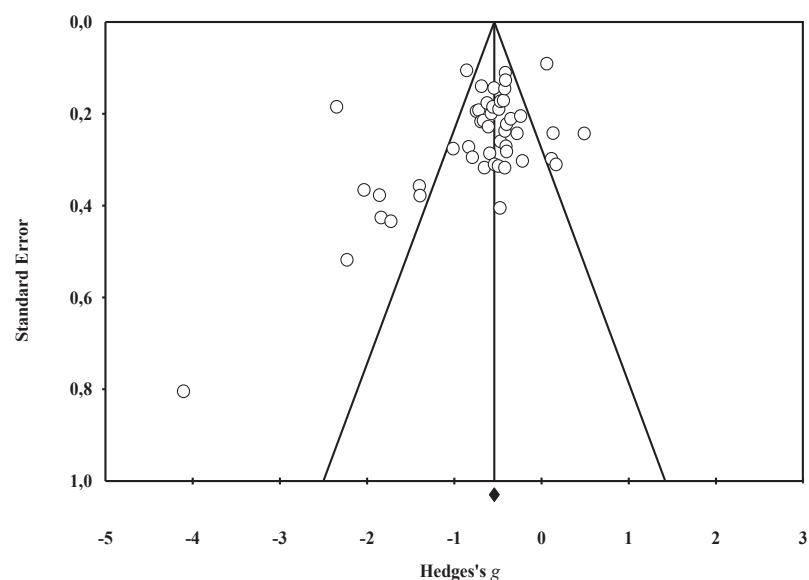


**Fig. 2** Funnel plot

with an effect size of zero that should be added to lose the significant result. All analyses have a *Fail-safe N* larger than the pre-set criterion, indicating that it is unlikely that the effect is only significant because of publication bias.

## Overall effect, effect of memory load, modality and timing of assessment

Analysis of data from 50 studies including 3,084 patients and 2,898 healthy controls on working memory averaged across tasks resulted in an overall moderate ES of -.65 ([−.80 to −.51], $p$ < .001) for lower working memory performance in stroke patients. Thirty-nine studies (78%) included a low-load working memory task. The analysis showed a moderate ES of -.58 ([-.77 to -.40], $p$ < .001). Analysis of forty-one studies (82%) with a high-load working memory task resulted in a comparable ES of -.59 ([-.73 to -.45]), $p$ < .001). Figures 3 and 4 show the effect sizes per study grouped by modality under high and low-load conditions separately. Analyses show medium effect sizes (< -.50) in the verbal domain for high-load (-.63) and low-load (-.53) tasks and for low-load (-.62) tasks in the non-verbal domain. For high-load non-verbal tasks the effect size was slightly lower (-.43). In order to compare the effect of low- and high-load we needed to assume independence of outcome measures. A mixed-effects meta-analysis shows a $Q$ statistic for the difference between the effect-sizes of .009 ($p$ = .922), indicating that there were neither differences in effect sizes between low- and high-load tasks, nor differences in effect sizes for non-verbal and verbal tasks (high-load $Q$ = 2.16, $p$ = .142; low-load $Q$ = .24, $p$ = .626). To examine the effect of interval between stroke onset and assessment, a secondary analysis was performed. For this analysis we excluded studies that analysed patients in the sub-acute and chronic stage as one group. Fourteen studies (28%) included patients in the sub-acute stage. The analysis showed a moderate ES of -.43 ([-.68 to -.19], $p$ < .001). For patients in the chronic stage ($k$ = 22, 44%) the ES was large, -.90 ([-1.15 to -.65], $p$ < .001, Fig. 5). A mixed-effects analysis showed that this difference in effect-sizes is statistically significant, $Q$ = 6.88, $p$ = .009. Patients in the chronic stage show more decrement in working memory performance compared to healthy controls than patients in the sub-acute stage. The heterogeneity indices ($Q$) were all statistically significant ($p$ < .05) for all analyses, indicating variation in study outcomes. The between study variance ($\tau^2$) of all studies is estimated as .21. The $I^2$ of 82.98 indicates that most of the observed variance reflects differences in study effect rather than sampling error. Results of the overall analysis and sub-analyses are presented in Table 1. Exclusion of studies that included patients with TIA did not lead to different results (Table S3a online supplemental materials). To minimize heterogeneity due to task variation, we reran the analysis including only studies with Digit Span and/or Spatial Span as working

memory measure. Effect sizes were highly similar to those of the analysis including all studies for the overall, and low- and high-load analyses. The sub-analysis with patients in the sub-acute stage included only eight studies and yielded a lower effect size (Table S3b online supplemental materials).

**Table 1** *Results of the meta-analyses.*

|  | k | N P/HC | ES (g) | 95% CI | Q | p (Q) | $I^2$ | $\tau^2$ | Fail-safe N |
|---|---|---|---|---|---|---|---|---|---|
| Overall | 50 | 3,084/ 2,898 | -.65 | -.80 to -.51 | 287.86 | <.001 | 82.98 | .21 | 4,949 |
| Low- load | 39 | 2,699/ 2,318 | -.58 | -.77 to -.40 | 308.16 | <.001 | 87.67 | .28 | 2,411 |
| High- load | 41 | 2,475/ 2,308 | -.59 | -.73 to -.45 | 171.72 | <.001 | 76.71 | .14 | 2,783 |
| Sub-acute | 14 | 830/ 466 | -.43 | -.68 to -.19 | 45.80 | <.001 | 71.62 | .15 | 144 |
| Chronic | 22 | 1,165/ 1,377 | -.90 | -1.15 to -.65 | 157.25 | <.001 | 86.65 | .29 | 1,740 |

*Note.* k = number of studies; P = patients; HC = healthy controls

### Figures 3-5 in supplementary materials

**Fig. 3** Performance on low-load tasks categorized by modality (verbal and non-verbal)
**Fig. 4** Performance on high-load tasks categorized by modality (verbal and non-verbal)
**Fig. 5** Overall working memory performance categorized by interval between stroke and assessment (sub-acute < 3 months and chronic)

### Qualitative assessment of studies comparing lesion location and longitudinal studies

This qualitative assessment includes 75 studies, 50 from the meta-analysis and 25 additional studies that were not taken into account in the meta-analysis due to missing statistics or overlapping samples. Sixteen percent of the studies (*k* = 12) compared working memory performance of patients with a left hemisphere stroke to patients with a right hemisphere stroke. Two-third of them (66.7%, *k* = 8) did not report a statistically significant difference in performance between left and right hemisphere stroke patients. Twenty-five percent (*k* = 3) reported a worse performance in left hemisphere stroke patients compared to right hemisphere stroke patients and controls on immediate serial recall tasks (Ho, Kong, & Koon, 2018), on letter-number sequencing (Andrews et al., 2014), and on a visually presented digit span forward and backward task (Low et al., 2016). One study (8.3%) reported no difference in performance of left hemisphere stroke patients and controls but impaired performance in right hemisphere stroke patients on a backward spatial span task (Van der Ham et al., 2012).

A second comparison made in studies is between patients with an anterior and posterior lesion. Studies showed performance more strongly affected in patients with frontal lesions compared to posterior lesions on different forward span tasks (Roussel et al., 2012), on digit span backward (but not forward, Leskelä et al., 1999), and on high-load n-back tasks (Andrews et al., 2013). In contrast, two studies reported the opposite; one reported performance in the posterior group to be inferior to patients with anterior lesions on digit span forward, with no differences on spatial span (Beeson, Bayles, Rubens, & Kaszniak, 1993). The other study reported lower performance in patients with inferior parietal lesions comparedto inferior frontal lesions on several forward span tasks (Baldo & Dronkers, 2006).

Whereas 59 studies used neuroimaging to confirm stroke, to check for exclusion criteria and to describe the sample or to create subgroups, only seven studies related specific lesion locations to working memory performance. Spatial working memory performance was associated with lesions in the right posterior parietal and right dorsolateral prefrontal cortex and bilaterally in the hippocampal formation (Van Asselen et al., 2006). Both parietal white matter and insula lesions were associated with spatial working memory deficits in neglect patients (Malhotra et al., 2005). Not only spatial, but also verbal short-term memory was associated with parietal lesions. Lesions in the insula were in the same study associated with a lower performance in a musical working memory task (Hirel et al., 2017). Another study demonstrated that high-load working memory tasks were associated with lesions in both the frontobasal and posterior centrum semi-ovale regions (Roussel et al., 2012). A study that only included patients with frontal lesions reported that the posterior part of the left middle frontal gyrus is significant for high-load but not for low-load working memory tasks (Volle et al., 2008). A study with patients with cerebellar lesions attributed filtering of information in working memory tasks, but not working memory capacity, to specific areas of the cerebellum, such as the tonsil, the inferior semilunar lobule, and parts of the vermal pyramid (Baier, Müller, & Dieterich, 2014). Finally, one study reported no predictive effect of lesion topography on memory. However, this study used a combined measure of spatial and verbal recall, recognition and working memory (Ramsey et al., 2017). Figure 6 shows how the results of these neuroimaging studies relate to each other.

Concerning timing of post-stroke working memory assessment, only four studies employed a longitudinal design. Three of these did not find any difference in performance of patients between the different time points. Two of these studies assessed the patients in the first week after stroke, with a follow up at three and six months respectively (Su et al., 2018; Van Zandvoort, De Haan, & Kappelle, 2001). The third study performed the first assessment between three and six months, with a three-year follow-up (Sachdev et al., 2009). The fourth study

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reported improved performance measured over three intervals; at two weeks, three months, and 12 months (Ramsey et al., 2017).
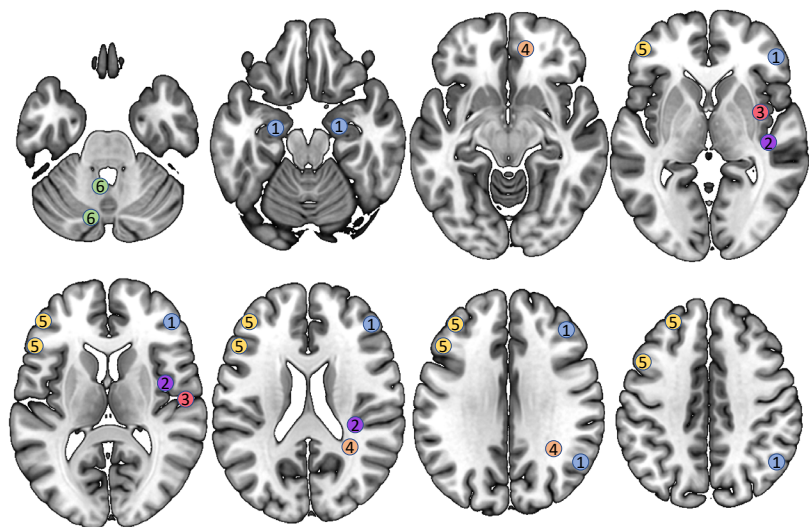


Fig. 6 Neural correlates associated with working memory performance

Note:
1. Van Asselen et al., 2006, anatomical description: posterior parietal cortex and dorsolateral prefrontal cortex in the right hemisphere, hippocampal formation bilateral
2. Malhotra et al., 2005, MNI coordinates: x = 35, y = -30, z = 24; x = 44, y = -12, z = 16, x = 43, y = -19, z = 04
3. Hirel et al., 2017, MNI coordinates: x = 59, y = -12, z = 11; x = 39, y = -2, z = -6
4. Roussel et al., 2012, anatomical description: frontobasal and posterior centrum semi-ovale regions in the right hemisphere
5. Volle et al., 2008, Brodmann areas: 6, 8, 9, 44, 45, 46
6. Baier et al., 2014, MNI coordinates: x=−6, y=−53, z=−39; x=−8, y=−73, z=−42; x=−9, y=−71, z=−42; x=−5, y=−67, z=−42.

## Discussion

This comprehensive review investigated working memory function post-stroke in comparison to healthy controls. A narrative and quantitative meta-analytic approach were combined. This allowed us to include studies of which we could not retrieve the necessary statistics for a meta-analysis but that did compare patients and controls on working memory performance. A meta-analytic approach was used for quantification of severity of working memory deficits after stroke. In addition, it allowed for a comparison of the effect of high- and low-load conditions, and of

verbal and non-verbal tasks, in the sub-acute and chronic stages. The literature was systematically reviewed to gain insight in the effect of lesion location on working memory and findings from longitudinal studies. Of the 75 studies incorporated in this review, 50 studies were included in the meta-analysis. The meta-analysis revealed a moderate overall effect size, indicating lower working memory performance in post-stroke patients relative to stroke-free controls.

Categorical analyses showed that performance on low-load working memory tasks was impaired to the same extent as the performance on high-load tasks. This is in line with the study by Roussel and colleagues (2012) who concluded in their study that working memory deficits are a consequence of reduced short-term memory capacity. Their conclusion is based on the finding that when controlling for verbal memory span, the impairment on working memory span disappeared. In terms of the model by Baddeley and Hitch (1974), this indicates impairment in stroke patients in the phonological loop and visuospatial sketchpad rather than the central executive. However, as most of the high load tasks are a form of backward span tasks, it can be argued that the tax on the central executive is low as the serial order stays the same and only needs to be reversed. Especially for spatial span tasks, it has been suggested that this process may only rely on the visuo-spatial sketchpad, as the visual pattern is not affected by reversing (e.g. Kessels, Van den Berg, & Brands, 2008; Wilde, Strauss, & Tulsky, 2004). The few studies in this review that included tasks with higher demands (n-back tasks and letter-number sequencing) show inconsistent results Three out of seven studies had considerable larger effect sizes and four had effect sizes comparable to the mean. Based on the current limited evidence, we have no strong reason to assume an additive deficit in more complex processing. However, the question of whether stroke results in an additive deficit in the central executive under more demanding conditions needs further investigation.

Stroke seems to affect both slave systems, the phonological loop and the visuo-spatial sketchpad, to the same extent. Effect sizes were comparable for verbal and non-verbal tasks. Out of 12 studies that compared patients with left and right hemispheric stroke, eight did not report differences in performance based on hemisphere of the lesion. This is not in line with the theory of hemispheric specialization, which predicts more severe impairments in verbal working memory in patients with a left hemisphere stroke and more spatial working memory impairments in patients with right hemisphere stroke (e.g. Habib, Nyberg, & Tulving, 2003). However, studies that did report a difference were in concordance with the theory of hemispheric specialization; one reported inferior performance in right hemisphere lesioned patients on a spatial task, three reported inferior performance on verbal tasks in patients with left hemisphere stroke. Based on the studies reviewed here we conclude that both frontal and non-frontal lesions,

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especially posterior parietal lesions, affect working memory performance. However, as with effect of hemisphere, there is no consensus on specialized areas depending on working memory task characteristics. A recent study indicates that whereas visual and motor deficits can be well explained by lesion characteristics, visual and verbal memory deficits are better predicted by measures of functional connectivity (Siegel et al., 2016). Our results support the view of a bilateral fronto-parietal network involved in working memory. Involvement of a widespread network might explain the high frequency of working memory deficits after stroke and the global nature of working memory impairment that we show in our meta-analysis.

Concerning the possible moderating effect of time between stroke and assessment, the meta-analysis and systematic review resulted in different conclusions. The meta-analysis showed a larger effect size in patients in the chronic stage of stroke compared to the sub-acute stage. This can be interpreted in different ways. First, remote effects may increase over time. A recent longitudinal study with MRI scans at one month, three months and twelve months after stroke, showed secondary degeneration in the limbic system and increased mean diffusivity after cortical stroke, independent of lesion location. The clinical outcome measure was the National Institutes of Health Stroke Scale (NIHSS) score, which did improve during the follow-up (Haque et al., 2019). No cognitive measures were taken in this study. Lower remote white matter integrity was related to worse long-term cognitive performance in a study with a follow-up 11 years after stroke (Schaapsmeerders et al., 2016). Second, selection bias may play a role. In the acute stage, patients with more extensive lesions or severe aphasia are less likely to be included in research, whereas they may be able to participate in research months later. This might lead to underestimation of working memory deficits in the acute stage. In addition, patients with good recovery might not participate months after the event, because they resumed their daily activities. Of the four longitudinal studies included in our review, three showed impaired performance in working memory that remained stable up to three years after the event. One longitudinal study showed spontaneous recovery with performance improving over the course of one year.

To pull apart these different explanations and gain more insight in the time-course of working memory deficits after stroke, more longitudinal research is needed. A limitation of the studies in the current meta-analysis is that they did not allow for a more fine-grained analysis of the effect of post-stroke interval. As the range of intervals within studies was very high, a categorical comparison was more informative. A second study-related limitation is that many studies did not specify whether they included patients with pre-existing cognitive decline that could have influenced working memory performance. With respect to the current review, a limitation is that only Pubmed was used for the systematic search. Future

studies should focus more on structural and functional connectivity in relation to working memory performance after stroke. These techniques could help to identify who is at risk for little spontaneous recovery or even deterioration in working memory and thereby guide rehabilitation programmes.

## Conclusion

Taken together, this meta-analysis and systematic review clearly demonstrate the global nature of the impairment in working memory post-stroke. All subsystems of working memory are affected evidently and similar findings were reported for non-verbal and verbal tasks. Lesions in a widespread fronto-parietal network result in working memory impairment, which in turn results in a reduced capability to maintain verbal and non-verbal information. The finding that effect sizes are larger in the chronic stage compared to the sub-acute stage and that most longitudinal studies show no improvement in working memory performance, is important to take into account when discussing future prognosis with patients.

## Supplementary materials

Figures 3-5
Appendix A PRISMA Checklist
Appendix B Adapted RTI Item Bank for Assessing Risk of Bias and Confounding
S1. Overview of articles included
S2. RTI items rated for all studies
S3.  Additional results: sub-analyses

# Chapter 6

## Long-term forgetting in stroke patients and healthy controls

## Abstract

Deficits in episodic memory are frequent complications after ischemic stroke. In standard clinical care episodic memory is assessed after a 20-30 minute delay. Abnormal memory decay over this period is characterized as rapid forgetting (RF). Previous studies have provided evidence of abnormal forgetting over a prolonged interval (days to weeks) despite normal acquisition, referred to as accelerated long-term forgetting (ALF). This study examined whether accelerated long-term forgetting (ALF) is present in stroke patients ($N$=91) using an acquisition phase followed by a recognition test immediately after encoding (T1), after a short delay (20-30 minutes, T2), and after a prolonged delay (one week, T3). Based on performance compared to age-matched healthy controls ($N$=85), patients were divided into three sub-groups: 1) patients without forgetting (no forgetting; NF), 2) patients with rapid forgetting (RF) between T1 and T2, and 3) patients with ALF. Furthermore, as a proxy of memory strength, confidence ratings were included. We demonstrate that ALF is present in a moderate amount of stroke patients. With 17% of the patients showing abnormal forgetting on a one-week delay without showing deviating scores on the standard delay, ALF appears to be even more prevalent in our stroke sample than rapid forgetting after a 20-30 minute delay (which was found in only 13% of our patients). Patients reported a lower confidence for their responses, independent of their actual performance. Adding a one-week delayed measurement may potentially assist in identifying patients with memory decrements that go undetected after 20-30 min delayed testing.

## Introduction

Deficits in episodic memory are among the frequent complications after ischaemic stroke (Snaphaan & de Leeuw, 2007). Depending on the location, volume, and number of infarcts, encoding, consolidation and/or retrieval of verbal and visual information may be compromised (Lim & Alexander, 2009; Saczynski et al., 2009). Most episodic memory tasks rely on an acquisition phase, followed by an immediate recall test and/or recognition trial (T1), as well as a delayed recall test and/or recognition trial after approximately 20-30 minutes (T2) in order to assess long-term memory retrieval (Lezak & Howieson, 2012). Such a 20-30 minute delay, however, may be too short to capture all deficits in long-term memory processes. This might partly explain why subjective memory complaints that are often reported after stroke are not always fully substantiated by performance measures, especially in the case of accelerated long-term forgetting (ALF; Butler & Zeman, 2008; Elliott, Isaac, & Muhlert, 2014; Geurts, van der Werf, Kwa, & Kessels, 2019).

The concept of ALF refers to abnormal forgetting over long delays (days to weeks) despite normal acquisition and unimpaired initial consolidation (Elliott et al., 2014). ALF is assessed by adding a distant third delayed test (T3) for recall/recognition. Individuals with ALF typically perform in the normal range on T1 and T2, but show significant impairments at T3 when compared to controls. Decreased performance, specifically at T3 (i.e., the presence of ALF), may reflect deficits in later stages of memory formation that are not captured with the standard delay of 20-30 minutes (Geurts, van der Werf, & Kessels, 2015). In the field of epilepsy, different time intervals, ranging from one day to six weeks, have been studied in relation to ALF (Hoefeijzers, Dewar, Della Sala, Zeman, & Butler, 2013). The addition of such a long-delay measurement increased the sensitivity of memory tasks to identify patients with left temporal lobe epilepsy who experienced memory complaints in daily life (Blake, Wroe, Breen, & McCarthy, 2000). The patients performed in the unimpaired range on standard neuropsychological memory assessments, while showing significant increased long-term forgetting after an 8-week delay on a verbal memory task. Similarly, Fitzgerald, Thayer, Mohamed, and Miller (2013) found that the performance on a verbal memory task with extended delays of 24 hours and 4 days was related to self-reported everyday memory complaints, whereas a 30-minute delay was not correlated with these complaints.

The underlying rationale is that during system consolidation, the circuitry that supports the memory reorganizes over time (Squire, Genzel, Wixted, & Morris, 2015). Different theories on memory consolidation diverge on their views on the reliance of memories on the hippocampus over time. During a 20-30-minute interval after initial encoding consolidation may already take place (Dudai, 2012),

but the time frame of the full consolidation process is unclear and might even be an ongoing process in which remote memories may continue to recruit hippocampal processing when retrieved (Dudai, 2012; Sekeres, Moscovitch, & Winocur, 2017). Since consolidation extends over such a protracted period of time, it is likely that the current default delay of 20-30 minutes does not cover all implicated memory processes.

There are currently two accounts for ALF compared to classic hippocampal amnesia, the latter being characterized by *rapid* forgetting (i.e., decay which is already present after a 20-30-minute delay, which for instance is observed in Alzheimer's dementia; Weintraub, Wicklund, & Salmon, 2012). The *qualitative* difference account suggests that ALF and classic hippocampal amnesia are two functionally distinct deficits, caused by different underlying mechanism (e.g. Fitzgerald et al., 2013). In this single dissociation, ALF patients show a similar memory performance at T2 compared to healthy individuals, but faster forgetting over longer delays. According to the *quantitative* difference account, ALF is forgetting that starts with subtle early retention deficits that progressively accelerate (Cassel & Kopelman, 2019; Cassel, Morris, Koutroumanidis, & Kopelman, 2016). This account states that classic hippocampal amnesia and ALF only differ with respect to their severity. It might be that the strength of the memory representation in ALF patients is already weaker at T2, yet not significantly different, as a decline in accuracy may be too subtle to be detected.

An indirect proxy for the strength of a memory can be obtained from a measure of accuracy combined with a confidence rating (Migo, Mayes, & Montaldi, 2012). Higher confidence ratings are more often based on recollection or strong familiarity, while lower confidence ratings are almost entirely based on weaker familiarity (Migo et al., 2012). Although differences in memory confidence ratings are often related to accurate or inaccurate responding, several studies show that some participants tend to express more confidence than others, unrelated to their accuracy but dependent on subject-specific factors (e.g. Kantner & Dobbins, 2019; Kantner & Lindsay, 2014; Kelemen, Frost, & Weaver, 2000). A factor that is possibly related to confidence is the perception of one's own memory functioning (i.e., meta-memory; Geurts et al., 2019)) demonstrated that TIA and minor stroke patients who performed normally after a short delay performed significantly worse than controls on a verbal memory task one week later. However, these patients did not report more memory complaints than controls. In fact, patients who reported to be more content with their memory actually showed *more* forgetting over time. In contrast, healthy controls who were more content with their memory showed *less* forgetting over time. The authors suggest that healthy controls may be better at estimating their own memory functioning in comparison to the patients, but confidence ratings were not included in that study. Confidence

ratings independent of accuracy give insight in subject-related factors, like perceived memory function, while the relation between accuracy and confidence provides information on memory strength.

So far, research into ALF in stroke patients is limited. The aim of the present study is twofold. One is to provide more insight into the prevalence of ALF after stroke. The second is to assess the relationship between memory performance and confidence ratings after different delays. To this end, a newly devised online set-up of a visual recognition task was administered in a large post-stroke patient group with supratentorial lesions. On the one hand, stroke may result in wide-spread disruptions of network activation, independent of the exact location of the lesion, on the other hand, stroke results in focal lesions that may be in a key region for episodic memory (Adhikari et al., 2017). Consequently, we hypothesize that episodic memory function can differ *between* stroke patients as a group and healthy controls, but also *within* stroke patients. Therefore, healthy participants were compared to stroke patients as one group, and to patients divided into three sub-groups: 1) patients without forgetting (no forgetting; NF), 2) patients with rapid forgetting (RF) between T1 and T2, 3) patients with ALF.

First, we hypothesize that a 1-week delayed measurement (T3) using a recognition task has added value for the detection of memory deficits that remain undetected with the standard 20-30-minute delay. Second, we expect that with increased delay duration confidence rates decrease, especially in patients with low memory performance.

## Methods

### Study Design
Data collection was part of the multi-center cohort study 'A functional Architecture of the Brain for Vision' (FAB4V) with the aim of assessing visual deficits in patients with ischemic stroke. Patients were admitted to one of the following hospitals in the Netherlands: University Medical Center Groningen (UMCG), Amsterdam University Medical Center (AmsterdamUMC), Radboud University Medical Center (Radboudumc), University Medical Center Utrecht (UMCU), Onze Lieve Vrouwe Gasthuis (OLVG), Maasziekenhuis Pantein, Rijnstate, Ommelander Ziekenhuis Groep and St. Antonius Ziekenhuis and Diaconessenhuis. The assessment took place at either the UMCG, AmsterdamUMC, Radboudumc or the UMCU between September 2015 and February 2020. The study was approved by the Medical Ethics Review Committee Utrecht (METC-No. 2015.372).

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## Participants

Consecutive patients with a diagnosis of ischemic stroke were recruited for this study. Inclusion criteria were: (1) the presence of a symptomatic cerebral (cortical or subcortical) ischemic stroke, diagnosed by a neurologist, (2) age between 18 and 90 and (3) fluent in Dutch. Exclusion criteria were: (1) diagnosis of another neurological disease than an ischemic stroke, (2) diagnosis of a non-neurological disease that affects cognitive function, (3) history of substance abuse, (4) history of cognitive decline or impairment in daily life prior to the stroke, (5) presence of severe disturbances in consciousness or comprehension to the extent that task instructions could not be understood and (6) MRI contraindications such as metal implants and claustrophobia. The assessment took place between two weeks and two years post-stroke.

A healthy control group, matched on age, was recruited without a history of any neurological diseases and psychiatric disorders that affect cognitive function and without a history of substance abuse. Written informed consents in accordance with the Declaration of Helsinki were obtained from all participants.

## Memory assessment and procedure

To assess ALF in visual episodic memory, we developed a computerized variant of the Doors Test (Schouten, Schiemanck, Brand, & Post, 2009), which is a subtest of the Doors and People Test (Baddeley, Emslie, & Nimmo-Smith, 2006). It consists of a four-alternative forced-choice paradigm, in which participants have to select a target picture of a door among three pictures of distractor doors (Fig. 1). For our paradigm, we selected fifteen target doors and ninety distractor doors from the doors database of the University of York (https://www.york.ac.uk/res/doors). This database contains 2,000 different doors, categorized on a range of variables including function, color, age, condition, shape, door opening, glazing type, surrounding and richness of detail. The fifteen target doors consecutively appeared in a random order at the centre of a white computer screen. Each target door remained visible for 5 seconds. After the series of fifteen target doors, a series of fifteen four-alternative forced-choice arrays followed (T1). For each array, the patient had 13 seconds to select the target door from the distractors, by pressing 1, 2, 3 or 4 on the keyboard. In each array, the target door was matched with three distracter doors based on similarity in color, shape and background details. After each response, participants indicated the confidence of their answer (1: 'Very confident', 2: 'Quite confident', 3: 'Not confident' or 4: 'It was a guess').

After a 20-30 minute delay, participants were asked to identify the 15 target doors in a four-alternative forced-choice array including a new set of distractor doors (T2). After a mean delay of 7 days [range 5 – 13 days], all participants were called by telephone and asked to open a link to the online version of the delayed



**Fig. 1.** Doors paradigm used in this study. On the left the encoding samples only presented at T1, followed by one trial of the recognition memory task for each of the time measurements, in which the participant needs to identify the target amongst three distractors and give a confidence rating.

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Doors test that was sent by email. They were asked to immediately complete this test. Again, participants had to identify the 15 target doors in a four-alternative forced-choice array (with a new set of distractor doors, T3). Participants were informed beforehand about the phone call, to ensure they were home and able to take the test. However, participants were not informed of the exact nature of the phone call (they were told we had some additional questions).

## Statistical analyses
### Forgetting scores
In this study we used forgetting scores, calculated relative to T1 as general baseline. The forgetting scores reflect the forgotten items as a percentage of the items that are acquired at T1 and are calculated with Equations 1 and 2.

T2 forgetting score = ((hits at T1 - hits at T2) / hits at T1)×100          (1)
T3 forgetting score = ((hits at T1 - hits at T3) / hits at T1)×100          (2)

The recognition task has a four-item forced-choice design, therefore it might be that participants performed better at T2 or T3 compared to T1. As we are interested in forgetting after initial acquisition, negative forgetting scores were set to 0, indicating that 0% of the initially learned items are forgotten.

In order to compare the increase in the proportion of forgotten items from T1 to T2, and T1 to T3, we performed a mixed-model ANOVA with T2 forgetting score and T3 forgetting score as within-subject factor and group (all patients taken together versus controls) as between subject factor. Effect sizes were computed with $\eta_p^2$. Bonferroni-corrected pairwise comparisons were used in case of a significant main effect of time. In case of violation of the assumption of sphericity Greenhouse-Geisser correction was applied.

Prevalence of RF and ALF within the patient group was calculated based on the performance of the stroke-free control group. A patient was identified with RF when he/she scored *below* 2 standard deviations of the mean of the control group on the T2 forgetting score. A patient was labeled as having ALF when he/she scored *within* 2 standard deviations from the mean of the control group on the T2 forgetting score and had a T3 forgetting score of *more than* 1.5 standard deviations above the mean of the T3 forgetting score of the control group (deviating forgetting score).

Comparability of the demographic characteristics of the patients without forgetting, patients with RF, patients with ALF, and healthy controls was assessed using one-way ANOVAs and chi-squared tests.

### Confidence ratings
To establish the relative influences of memory accuracy, delay interval, and participant group (healthy controls, NF patients, RF patients, ALF patients) on memory confidence we calculated the mean confidence for every participant for the trials with correct responses and those with incorrect responses. To assess how much participants adjust their judgment based on accuracy, a slope was calculated by subtracting the mean confidence for trials with correct responses from the mean for the trials with incorrect responses, per participant per time measurement.

Subsequently, two mixed-model ANOVAs were performed to test for the effect of group (healthy controls, NF patients, RF patients, ALF patients), and time (T1, T2, T3), on confidence ratings. Outcome measures were 1) the mean confidence rating, independent of accuracy and 2) the slope indicating the difference in confidence ratings between errors and hits. In case of significant main effects, Bonferroni-corrected pairwise comparisons were used to assess which moments of measurement or groups differed.

### Imputation of missing data
Due to software complications there was a small amount of missing data for hits and errors in our sample. A total of 25 values were missing. At T1, 7 values were missing divided over 5 trials. At T2, 12 values were missing divided over 7 trials. At T3, 5 values were missing divided over 3 trials. As the missing data were completely at random (MCAR), we used the multiple imputation method for imputation, with age, education, sex, group and scores (hits/misses) on every single item as predictors.

## Results

### Stroke patients versus healthy controls
A total of 91 stroke patients and 85 age-matched healthy controls were included in the study. There was no statistically significant difference in forgetting rates between controls and patients when all patients are taken together [$F_{(1, 174)}$ = .91, $p$ = .341, $\eta_p^2$ = .005]. A significant main effect of measurement time was found [$F_{(1, 174)}$ = 68.5, $p < .001$, $\eta_p^2$ = .283]. Both patients and controls had greater forgetting scores at T3 compared to T2. There was no time of measurement by group interaction effect [$F_{(1, 174)}$ = .021, $p$ = .885, $\eta_p^2$ = .000].

## Patient sub-groups

Prevalence of three different patterns of forgetting was examined. 15 patients (17%) showed ALF. They performed in the normal range on the T2 forgetting score, whereas their T3 forgetting scores were below1.5 standard deviation from the mean of the control group. Twelve patients (13%) showed RF at T2. Sixty-three patients (70%) showed NF, as they had normal forgetting scores on both T2 and T3 compared to a healthy control group (see Table 1 for demographics of the patient sub-groups and healthy controls). Figure 2 shows the mean hits of the four sub-groups per time of measurement.

**Table 1.** Demographical characteristics of the no-forgetting patient group (NF), the patients with rapid forgetting (RF), the patients with accelerated long-term forgetting (ALF), and the healthy controls

|  | NF patients (*N* = 64) | RF patients (*N* = 12) | ALF patients (*N* = 15) | Controls (*N* = 85) | *P* value |
|---|---|---|---|---|---|
| Age mean ± sd | 62.3 ± 10.8 | 60.8 ± 6.4 | 66.9 ± 9. 11.7 | 62.0 ± 11.4 | .399 |
| Sex (m/f) | 43/21 | 11/1 | 9/6 | 42/43 | .016 |
| Education Mean ± sd | 5.6 ± 1.1 | 5.3 ± 1.8 | 4.9 ± 1.8 | 5.7 ± 0.9 | .047 |

*Note.* Education level was based on the Dutch educational system, with 7 categories (Verhage, 1964), from 1 (primary education) to 7 (university education).

## Confidence ratings

For mean confidence scores, independent of accuracy, a significant main effect of time of measurement was found [$F_{(1.62, 278.8)}$ = 34.6, $p < .001$, $\eta_p^2$ = .167]. Pairwise comparisons showed that mean confidence scores decreased from T1 to T2 ($p$ = .002), from T1 to T3 ($p < .001$) and from T2 to T3 ($p < .001$). A significant main effect for group was found [$F_{(3, 172)}$ = 7.1, $p < .001$, $\eta p^2$ = .110]. Healthy controls were more confident than NF patients ($p$ = .002), RF patients ($p$ = .023) and ALF patients ($p$ = .027). No significant differences in confident ratings were found between the three subtypes of patients. No significant time by group interaction effect was found [$F_{(1, 174)}$ = .02, $p$ = .885, $\eta_p^2$= .000].

Analysis of the slopes (see Fig. 3), indicating the difference in confidence per correct versus incorrect responses, showed a significant main effect of time of measurement [$F_{(2, 304)}$ = 6.64, $p$ = .002, $\eta_p^2$ = .283]. Pairwise comparisons showed that the slopes at T3 significantly differed from those at T1 ($p$ = .010) and T2 ($p$ = .003), whereas there was no difference between those at T1 and T2. At T3,
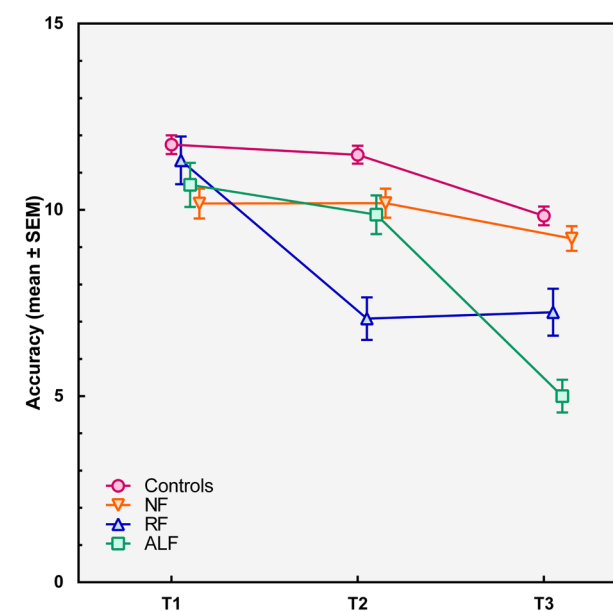


Fig. 2: Recognition accuracy (means ± standard errors of the mean) immediately after the encoding phase (T1), after 20-30 min (T2) and after one week (T3) for the no-forgetting patient group (NF), the patients with rapid forgetting (RF), the patients with accelerated long-term forgetting (ALF), and the healthy controls

the difference in confidence scores between correct and incorrect responses was smaller than at T1 and T2. Neither a main effect of group [$F_{(3, 152)}$ = 1.77, $p$ = .156, $\eta_p^2$ = .034], nor an interaction effect of time of measurement by group was found [$F_{(6, 304)}$ = .56, $p$ = .764, $\eta_p^2$= .011].
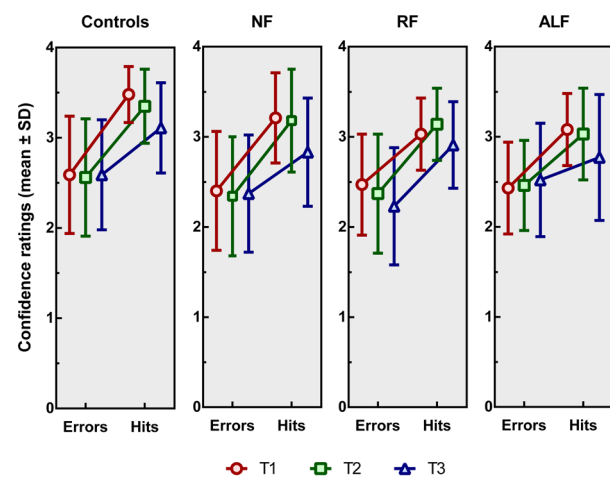
**Fig. 3.** Mean confidence ratings (± standard deviations) for the controls, the no-forgetting patients (NF), the patients showing rapid forgetting (RF) and those showing accelerated long-term forgetting (ALF) patients immediately after the encoding phase (T1), after 20-30 min (T2) and after one week (T3). The slope of each line reflects an increase in confidence based on correct versus incorrect responding.

## Discussion

In this study, we evaluated the prevalence of ALF after stroke in comparison to the prevalence of RF and normal forgetting (relative to stroke-free controls). Furthermore, we investigated the effect of a longer delay on meta-cognitive confidence for these participants groups, using a visual recognition memory paradigm.

We demonstrated that ALF is present in a moderate amount of stroke patients. With 17% of the patients showing abnormal forgetting after a one-week delay without showing deviating scores on the standard delay, ALF appears to be even more prevalent in our stroke sample than rapid forgetting shown already after a 20-30 minute delay (which was the case in 13% of the patients). Adding a one-week delayed measurement may thus potentially be valuable for the identification of patients with memory decrement that are missed in standard clinical practice where a 20-30 minute delay is the default. At group level, we did not find any significant differences in forgetting rates between stroke patients and controls. This is in line with previous findings on verbal recognition (as opposed to recall) tasks with a prolonged delay, where no difference was found between controls and patients with TIA or minor stroke (Geurts et al., 2019).

Our data support the notion by Fitzgerald et al. (2013) that ALF and RF are two distinct phenomena. This in contrast to the view of ALF as differing from RF only with respect to initial (i.e. at T2) severity of forgetting, as argued by Cassel et al. (2016) and Cassel and Kopelman (2019). In our sample, patients with ALF and RF show very different patterns of forgetting. Stroke patients who demonstrate ALF showed similar T2 forgetting rates as stroke-free individuals and stroke patients without memory problems, but high forgetting rates during the prolonged delay. In contrast, stroke patients with RF did not show any further decline after T2. Although it was expected that ALF patients did not significantly differ from patients without memory problems on T2 forgetting scores (as we defined both groups by the fact that they performed *within* 2 standard deviations from the mean of the control group), according to the quantitative theory one would expect that the strength of the memory representation in ALF patients is already weaker at T2, though very subtle (Mayes, Hunkin, Isaac, & Muhlert, 2019).

From a neural perspective, a qualitative difference between ALF and RF is also plausible. That is, RF has been associated with medial temporal lobe functioning (Squire et al., 2015), while ALF, as a deficit in the later stage of memory consolidation, might rely more on distributed cortical networks. Stroke lesions can be widely distributed across the brain, affecting both cortical and subcortical areas. Therefore, different patterns of memory deficits, such as RF and ALF, relying on (partly) different brain regions, may occur after stroke.

Regarding meta-cognitive confidence after stroke, stroke patients rate their memory confidence overall lower than healthy controls, regardless of their actual performance. An explanation for this finding may be that psychological and emotional effects of stroke may affect one's self-appraisal and confidence (Wei et al., 2016). Furthermore, in all participants (healthy controls and the three groups of stroke patients) confidence decreased when the delay after encoding increased. Visual inspection of the data suggests that ALF patients rated their own memory performance lower compared to the other subtypes of patients and healthy controls, although this finding was not statistically significant. Especially at the one-week delayed test, ALF patients seemed less confident when giving correct answers compared to the other participants. This might indicate that the correct responses of ALF patients are more often based on weak familiarity, while the correct responses of the other patients might be more often based on recollection or strong familiarity. As familiarity is an indirect proxy for weaker memory capacity (Migo et al., 2012), this finding complements our previous finding in such that memory of ALF patients is not only less accurate at T3 compared to other patients, but is also weaker. This, however, needs to be replicated and examined in more detail in future research.

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There are some limitations and strengths in the design of this study. A practical issue concerning recognition tasks in long-term forgetting is the effect of rehearsal that could be a result of (residual) learning capacity (Baddeley, Atkinson, Kemp, & Allen, 2019). However, as the aim of our research was to detect ALF, multiple tests for the same target items within the same person were necessary. Generally, this could result in a bias that patients with impaired learning capacity but normal rates of forgetting, are easily mistaken for ALF (Baddeley et al., 2019). However, our data do not show faster forgetting in poorer learning performers. Hits on T1 (learning capacity) did not predict the forgetting rates between T2-T3 in both the patient group and the healthy control group. Additionally, our data do not indicate a learning affect, as the control group did not show any increase in accuracy between T1, T2 and T3.

A second issue in memory research is that recognition tests are often less effortful and more susceptible for ceiling effects than recall tests, which could reduce the sensitivity of ALF measures (Elliott et al., 2014). Exploration of the distribution of the scores on T1, T2 and T3 in our sample, however, did not reveal any ceiling effects for any of the three time measurements. Furthermore, it is not possible to examine visual memory for stimuli such as the ones we used using a free-recall test.

A final important practical issue in ALF research concerns the debate on how forgetting rates can be compared when learning capacity may differ between groups (Loftus, 1985; Wheeler, Ewers, & Buonanno, 2003). As a solution for this problem, most studies assessed ALF after optimizing initial learning (Geurts et al., 2015), also called "learning to criterion". However, our data shows that initial learning does not substantial differ between our four groups. Therefore, we suggest that this potential confound has not affected the results of our study. Furthermore, a disadvantage of learning to criterion is that it may result in overlearning of the material, which, in turn, can lead to ceiling performances that mask early forgetting (Bell, 2006). In addition, optimizing initial learning does not reflect the learning and memory demands of most everyday situations (Geurts et al., 2019).

Future research should focus on anatomical correlates and functional connectivity to investigate networks underlying ALF and RF. In line with our suggestion that ALF and RF are two distinctive processes, relying on different parts of the brain, we expect disruptions in a distributed cortical network to be associated with ALF, while reduced functional connectivity between hippocampal areas and the cortex might be associated with RF. Based on the prevalence of both ALF and RF in stroke patients, stroke patients seem to be a suitable population for such network analysis.

In sum, ALF often remains undetected in clinical practice in which the standard delay for testing is typically 20-30 minutes. This study complements previous research demonstrating that ALF patients show clearly distinguishable forgetting patterns compared to RF patients. ALF and RF seem to be two functionally distinct deficits. With this new set-up of the Doors, wherein patients can perform the one-week delay in their home environment, ALF measurement becomes feasible for clinical practice.

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Chapter 7

Summary and Discussion

This thesis investigates subsystems of memory in the visual domain, using novel behavioral paradigms, lesion-symptom mapping, and computational modeling, in healthy adults and stroke patients. The relevance is twofold. One, subsystems of memory are typically studied in isolation complicating comparison between systems and their interrelationships. Two, theories of memory are predominantly based on studies using verbal materials, while our interactions with the world are in large part visual in nature. This final chapter provides an overview of the main results from the studies presented in this thesis and a discussion on how these results relate and contribute to theories on memory. In addition, methodological considerations are discussed, followed by clinical relevance and future perspectives.

## Main findings

In **chapter 2**, age-associated differences in visual working memory and episodic memory were examined in a single task design to investigate whether they are affected to a similar extent by aging. We introduced a task in which visual working memory and subsequent episodic memory performances were measured using the same stimuli. Overall, the results showed that older adults performed worse than younger adults on both tasks to a similar extent. Interestingly, performance on the working memory task and the subsequent episodic memory task was related in younger but not in older adults. The relationship between working memory and episodic memory differed as a function of age-group indicating that they are separate systems or rely on different processes.

In **chapter 3** the same task design was used in a population of stroke patients and stroke-free older adults. The aim was to contrast the theory of separate memory stores with the theory of working memory as activated long-term memory based on behavioral performance and lesion-behavior associations. Discriminability, the ability to distinguish between targets and non-targets, in working memory and episodic memory seemed different processes. Lesion-symptom mapping analyses suggested there might be different regions of the right arcuate fasciculus that are more strongly associated with visual working memory and episodic memory. Response bias, the tendency to answer more liberal or conservative, might be a shared process in working memory and episodic memory. These results give partial support for the multi-store view of memory.

Multi-store models of memory are characterized by the view of separate representations of materials in working memory and episodic memory. In c**hapter 4** we investigated visual representations in working memory. We examined whether stroke can result in selective impairments of feature binding, a cognitive process that is crucial for successful memory formation. A novel approach was used to

assess feature binding in visual working memory, using a short-delay reproduction task in combination with computational modeling and lesion analysis. Participants briefly viewed a sample array of colored disks, and then had to report a feature – color or location – of an item when cued with its other feature. Patients showed decreased memory precision for color and location, but no consistent binding deficit. Report precision and binding performance were associated with different lesion profiles. Our results suggest that memory representations are widely distributed in the brain and can be found across parietal, temporal, and frontal cortices. Representations in different areas might compensate for impaired encoding in lesioned areas as stroke patients demonstrated mostly subtle impairments in visual working memory.

Whereas the results of chapter 4 only showed mild impairment in visual working memory in stroke patients, **chapter 5** described a meta-analysis and systematic review on the severity and nature of post-stroke working memory deficits that concluded that stroke patients tend to have moderate deficits in working memory. Post-stroke working memory deficits were found to be global in nature; effect sizes were similar for low-load and high-load tasks, and for verbal and non-verbal material. Furthermore, working memory deficits remain prominent in the chronic stage of stroke. This review is the first to analyze all available studies in a stroke population that included a working memory measure and thereby providing insight in how different components of working memory are affected by stroke.

In a stroke population not only working memory deficits, but also episodic memory deficits are common. In **chapter 6**, we investigated the prevalence of different profiles of forgetting in episodic memory in stroke patients. Visual memory was assessed at three time-points: direct recognition (T1), short-delay recognition (20 minutes, T2), and long-delay recognition (one-week, T3). We defined three different profiles of forgetting in our stroke population based on performance relative to the control group: patients without memory impairment ($N$ = 64), patients with rapid forgetting ($N$ = 12), and patients with accelerated forgetting only on long delays ($N$ = 15). Furthermore, patients were less confident about their memory performance independent of their actual accuracy. As standard clinical practice is to assess episodic memory up to a 20-30 minute delay, a group of patients with memory decrements might be missed.

## General discussion

### Unitary and multicomponent models

Working memory and episodic memory are two different processes, although the nature of their interrelationship is debated. At the core of this debate lies the question whether a separate short-term store exist. According to the multi-component view of memory (Baddeley & Hitch, 1974), a separate store is needed to support memory for novel representations and perform variable bindings. Unitary theories, like the embedded processes model (Cowan, 1988), state that there is a single memory system with different levels of activation. Theories are primarily based on verbal memory experiments, even though they acknowledge that the same mechanisms might apply to other domains (Baddeley et al., 2019). Working memory and episodic memory have so far predominantly been studied in isolation, therefore reported differences in memory systems might be confounded by task characteristics. Both of these issues are addressed in two studies described in this thesis by using one task design to assess visual working memory and episodic memory for the same stimuli. By studying healthy older adults and stroke patients, we demonstrated that working memory and episodic memory performance act as independent systems, and that selective impairments in either working memory or episodic memory occur. That is, correct identification of targets on the working memory task had no influence on the accuracy on these items on subsequent memory task. This suggests the tasks may rely on different representations (but see discussion on this in the next section on encoding).

Analyses of performance in relation to lesion location also suggested distinct neural substrates for processes in working memory and episodic memory. Lesions in the anterior and long segment of the arcuate fasciculus in the right hemisphere were more strongly associated with discriminability in working memory than in subsequent memory, while lesions in the posterior segment of the arcuate fasciculus were more strongly associated with criterion setting in subsequent memory than in working memory. The arcuate fasciculus in the right hemisphere has been associated with visual working memory in previous studies but a possible gradient in the arcuate for different memory-related processes should be further investigated.

Overall, it can be tentatively concluded that some processes involved in working and in long-term memory rely on separate mechanisms, while acknowledging that there might also be processes shared between working memory and episodic memory (e.g. response bias).

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## The role of task characteristics in dissociations between episodic and working memory

In the debate on multi-store versus unitary models of memory, one of the arguments of proponents of the single-system view is that dissociations between working memory and episodic memory are confounded by differences in cognitive control and complexity of stimuli. Cowan (2019) argues that the nature of the encoding is different when preparing for short-term retention or for long-term retention. In verbal memory, when planning for long-term memory items are encoded in a semantic, more elaborative manner, while this may not be necessary for short-term retention, where phonological rehearsal might suffice (Craik & Watkins, 1973). Also, stimuli used in episodic memory tasks are often better suited for rich encoding (Cowan, 2019). In the combined task design that we developed, there is a single encoding phase so the stimuli for both tasks are identical. To prevent dual-task load in the working memory task, participants were only instructed on the demands of the working memory task and were not informed about the subsequent memory task before the encoding phase. Therefore, the encoding of the objects is not modulated by differences in strategy for encoding, making the task maximum sensitive for identifying shared processes in working memory and episodic memory, at the costs of less optimal encoding conditions for episodic memory. Our results suggest separate representations in working memory and episodic memory; even though the design stimulates a single encoding process, we still find no correlation in performance and some evidence for distinct neural substrates.

## The role of binding in working memory

Our combined task assessed temporal binding in the working memory task and spatial binding in the subsequent memory task. As we did not include a non-binding condition we cannot distinguish between memory for the individual objects and their bound representations. In a visual working memory task we conducted to assess feature binding, we can distinguish between memory for individual features and their bound representations. According to two recent computational models the key cause of binding errors between features is imprecision in memory for the cue feature (Oberauer & Lin, 2017; Schneegans & Bays, 2017). While some patient populations are characterized by specific binding deficits in absence from memory deficits for individual features (such as Alzheimer's disease and possibly patients with medial temporal lobe damage; Schneegans & Bays, 2019) our results show that in stroke patients binding is not specifically impaired. Selective binding deficits, reflected by more mis-bindings than expected based on accuracy for single features, were highly uncommon in both healthy aging and in stroke patients. Stroke patients, however, performed worse than controls in reporting single features. Results converge with the body of recent studies on aging and feature binding and extend previous findings to stroke patients.

## Distributed memory

Our results on neural substrates for feature binding converge with numerous studies in humans and non-human primates that have provided evidence for storage of working memory contents in multiple brain regions, from sensory to parietal and prefrontal cortex. There is a suggested gradient of level of abstraction, from low-level feature representations in sensory areas, to abstract and semantic representations in frontal regions (Christophel et al., 2017). Different representations supplement each other, augmenting the total information in working memory (Souza & Skóra, 2017). Representations from different areas in the brain might in part compensate for impaired encoding in lesioned areas. Following up on this, maybe the question of where memory is in the brain is not very informative. A better question would be: what are contributions of different regions and representations? On the one hand, this thesis shows that reduced precision in visual representations is associated with multiple bilateral frontoparietal areas in the brain (chapter 4). On the other hand, the location of stroke lesions seems to be only weakly related to reduced working memory and episodic memory performance (chapter 3). It has been demonstrated that while deficits in motor and visual impairments can be well explained by lesion location, visual and verbal memory functions were better explained by functional connectivity (Siegel et al., 2016). This indicates that short-term retention as in the feature binding task might be more closely related to visual functions, though the widespread regions associated with performance indicate that more processes are involved than just sensory representation. The 2-back task and subsequent memory task rely on multiple mental operations and therefore presumably on a more distributed network which cannot be identified by lesion-symptom mapping.

## Global and selective deficits

The presented meta-analysis in this thesis showed that lesions in a widespread frontoparietal network result in working memory impairment. A distributed network underlying memory function is in line with the global nature of memory impairments post-stroke. Stroke affects low-load (i.e. passive maintenance) and high-load (executively demanding) working memory in verbal and non-verbal domains to a similar extent. Compared to healthy controls the effects are of moderate magnitude and most studies show no improvement in working memory over time, stressing the severity of post-stroke working memory dysfunction.

In all experimental studies in this thesis we showed that, at the group level, controls outperform patients. We also identified selective deficits. Sixteen percent

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of our stroke population showed visual working memory impairment in absence of episodic memory impairment, or vice versa, as measured in one task design. A deficit in reporting visual features was present in 12% of a sample of stroke patients. Finally, the addition of a second delayed visual recognition test allowed for identification of 15 patients (16%) with accelerated forgetting only after a long delay, in addition to 12 patients (13%) who were identified as having memory deficits according to standard clinical procedures. In all, this thesis demonstrated that post-stroke visual memory deficits are common and can have many manifestations.

### Moving forward

To conclude, the research in this thesis demonstrates that different profiles of visual memory impairment can be identified in older adults and stroke patients, and that there are multiple distributed representations in the brain. Maybe than the question of how this relates to one shared or multiple separate storages, is not the right question to ask. I argue, as has also been suggested by others (e.g. Baddeley et al., 2019), that the debate on systems for working memory and episodic memory is at an impasse due to a lack of consensus on terminology and methodology. A large body of neuropsychological evidence, including results presented in this thesis, seems to be consistent with different theories, including the embedded model and the multicomponent model of memory. In order to move forward, collaborations between researchers with conflicting theoretical perspectives are essential. First attempts have been made to directly compare different theories using new task designs, within this thesis and outside (e.g. Doherty et al., 2019; Logie, 2019). So far, results have shown partial support for each of the models. It is important to keep in mind that the success of a theory of memory is in accounting for a wide range data from patients, healthy subjects, and different tasks, while at the same time generating testable hypothesis.

## Methodological considerations

### Comparing memory processes

Throughout this thesis, the main aim was to directly compare different memory processes: visual working memory and episodic memory (chapters 2 and 3), visual working memory for individual features and binding of features (chapter 4), low-load and high-load working memory for verbal and non-verbal materials (chapter 5), and forgetting of learned visual materials after shorter and longer delays (chapter 6). This aim is a challenging one, both for practical and theoretical reasons. A more extensive discussion on the pros and cons of specific designs

can be found in the associated chapters, here I will briefly address overarching issues.

Practical reasons complicating the comparison of working and episodic memory include task difficulty. To optimize performance, a balance is needed so a task does neither induce a floor effect in older adults or stroke patients, nor a ceiling effect in the control group. We succeeded in this for the task design in which we measured working memory with an object 2-back tasks, followed by a subsequent episodic memory task, and the Doors episodic memory task with three delays. In the delayed-reproduction task for feature binding, we found a low number of swap errors, indicating that the task was relatively easy for both controls and stroke patients. A second challenge is designing a paradigm that assesses two different processes with the only difference between the tasks being the processes of interest. This proved specifically difficult in the combined working memory and episodic memory task design keeping the previous argument on floor and ceiling effects in mind. This resulted in the use of different types of context binding (temporal versus spatial). A third practical limitation is the number of trials in relation to feasibility in patients and older adults (as more trials may substantially increase the assessment time, resulting in fatigue, especially in patients). This resulted in fewer trials and fewer different conditions in some tasks than what would have been desirable from a purely experimental perspective.

The biggest theoretical challenge is trying to assess the relationship between two concepts in different tasks or conditions, given that the key point of the theoretical debate is the question whether these two latent constructs are actually two different things at all. This discussion is relevant investigation for the research in my thesis, examining the relationship between working memory and episodic memory, and to a lesser extent, affecting the study on individual feature processing and feature binding. We assessed relationships between two processes on a behavioral and neural level and interpreted selective deficits, a lack of correlation, and separable neural substrates, as support for separate representations. It can be argued that these findings may also be explained by different control processes rather than different stores. Another theoretical consideration is the question when a visual task really relies on visual processing? Are some people more likely than others to apply a verbal strategy in a visual task? And is that an individual factor or are some groups (e.g. older adults or stroke patients) more inclined to use a specific strategy? These questions cannot all be answered in this thesis but are important to keep in mind when interpreting results. Finally, several group differences have been reported throughout this thesis. A fair question is how these should be interpreted given the sometimes substantial individual differences and large heterogeneity, especially in a stroke population. Accompanying group statistics with individual data showed where possible whether certain outcomes

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reflect an overall pattern or whether effects are driven by a selection of the group that might be further characterized. Group statistics, as for example those from the meta-analysis in chapter 5, give insight in a population as a whole, and emphasizes points of attention for clinical practice.

## Aging-associated differences

The ideal design to study life-span decline in visual memory and the relation between subsystems of memory is a longitudinal one. With a cross-sectional design as used in chapter 2, only age-associated differences can be identified. The older adults in this study are the same as the control group of chapter 3. This resulted in the control group being (slightly) older than the patient group, this might have led to an underestimation of actual differences between patients and controls. In the other chapters the stroke-free controls are age-matched to the patients.

## Stroke patients and lesion-symptom mapping

The advantage of studying stroke patients is that due to the sudden nature of the brain damage, it is acceptable to infer causal relations (Karnath, Sperber, Wiesen, & De Haan, 2019; Rorden & Karnath, 2004). This in contrast to functional neuroimaging studies in healthy participants were associations are correlational in nature, precluding any conclusions on causality. A second advantage is that post-stroke memory impairment is frequent (Snaphaan & De Leeuw, 2007) making it a feasible population to study brain-behavior relationships in this cognitive domain (also with potential clinical relevance).

There are also several limitations. First, as with our study on aging-associated differences in memory, the studies that concerned stroke patients all had a cross-sectional design. A consequence of this is that pre-stroke memory function is unknown. Stroke patients might have accumulated years of subclinical vascular injury which can be related to memory function (Van Leijsen et al., 2019). Second, there might be a selection bias in the sample with patients with mild symptoms and small lesions being more likely to participate in research, while patients with large lesions, or left hemispheric lesions resulting in aphasia, are underrepresented. Third, brain lesions due to stroke are determined by the vascularization of the brain, resulting in vulnerable lesion sites and uneven density of lesions across the brain. As a consequence, we can only draw conclusions about voxels and regions of interest with sufficient lesion coverage. Lesion-symptom mapping in the (sub) acute phase of stroke, can give insight in anatomical correlates of cognitive functions in the healthy brain, as we did in chapter 3. In chapter 4 we combined data from patients that underwent neuroimaging and assessment in the subacute stage, with patients with an MRI in the subacute stage and behavioral testing in

the chronic phase. As functions (at least partially) may recover due to reorganization of the brain and compensatory strategies, brain areas that are crucial for a function might be missed in the lesion-symptom mapping analysis. Only conclusions can be drawn about which lesion locations are associated with chronic deficits. This choice was based on practical considerations but remains suboptimal.

## Clinical relevance

Comparing healthy older participants and stroke patients to a control group, we found an overall decrement in all subsystems of memory we studied. A closer look revealed that subsystems can be selectively affected in both aging and post-stroke. Previous studies have indicated a discrepancy between highly prevalent subjective memory failures and objective memory performance after stroke (Maaijwee et al., 2014). This finding stresses the need for awareness of (subtle) memory impairments that might be missed in standard clinical care. Both verbal and visual memory over different delays should be assessed. The current standard is to test mostly for verbal materials and with a maximum delay of 30 minutes. This thesis demonstrates that memory impairment for visual information is common post-stroke. Furthermore, we showed there is a group of stroke patients that show accelerated forgetting only after a prolonged delay (one week) that is likely to be missed in general clinical practice.

Our findings support the notion of the distributed nature of neural correlates for visual memory. For representations in visual working memory we found multiple brain regions associated with performance. At the same time, we observed mostly subtle impairments. Representations from different areas in the brain might in part compensate for impaired encoding in lesioned areas. It has been suggested that representations in different regions might vary in different levels of abstraction, from sensory to abstract representations, and that verbal categorization augments visual processing. This suggests that mnemonic strategies might be beneficial for stroke patients with visual memory deficits. For face-name pairs, mnemonic strategy training has been shown effective in stroke patients (Batista et al., 2019). More elaborate research on this is needed.

At the group level, all our studies showed subtle differences between stroke patients and controls. This seems at odds with previous studies reporting high frequency of post-stroke dementia (for a meta-analysis see (Pendlebury & Rothwell, 2009). However, it is important to keep in mind that each of the studies presented in this thesis, also identified a subset of patients with clearly impaired performance. According to the meta-analysis by Pendlebury and Rothwell (2009), 10% of first-ever stroke patients develops dementia within one year. This is well in

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line with our findings of patients with impaired performance, though we did not study the development of dementia in our stroke cohort.

## Future perspectives

Although the studies described in this thesis contribute to the understanding of subsystems of memory, some recommendations for future research following up on our findings can be made. The results of chapter 2 show that working memory and episodic memory performance are correlated in younger, but not in older adults. Studies with a longitudinal design are needed to examine how the relationship between working and episodic memory changes over the life span, as these might provide insight into which processes are based on the same underlying neural substrates an which are separate for working memory and episodic memory.

Concerning stroke patients, our results show that specific impairments in different memory systems are common. Important for patient care is to know when reduced memory function based on assessment is experienced as an obstacle in daily life. Previous studies have shown that memory complaints in stroke patients are stronger associated with beliefs about one's memory functioning, than actual performance on a standard clinical episodic memory test (Aben et al., 2011). In epilepsy patients, objective accelerated forgetting is typically associated with subjective memory complaints (Fitzgerald, Mohamed, Ricci, Thayer, & Miller, 2013). Future studies should investigate what type of memory impairment is associated with everyday memory complaints in stroke patients.

Finally, it is not very straightforward who is at risk for (specific types of) post-stroke memory impairment. Findings from our study converge with previous reports that suggest that impaired memory function can only be explained by lesion location to a limited extent. Both for patient care, and our understanding of the functioning and organization of the healthy brain, future studies should be using a combined approach of behavioral assessment and structural and functional neuroimaging in stroke patients and heathy controls. In stroke patients, critical loci for a specific cognitive function can be identified. This can subsequently be used as a seed region for functional MRI in a healthy control group to investigate a functional network that might support this cognitive process. The other way around, functional neuroimaging in healthy individuals helps to identity brain regions or networks associated with cognitive functions, and these could be validated in a stroke population. Whether patients and controls are compared or different memory processes, using one paradigm for assessment of both is crucial.

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## Supplementary materials chapter 3

**S1.** List of number of subjects with a lesion per ROI

## Supplementary materials

List of number of subjects with a lesion per ROI. Only ROIs in which at least four subjects had a lesion were included in the atlas-based analyses.

| GLASSER atlas | | | Left | Right |
|---|---|---|---|---|
| 1 | V1 | Primary Visual Cortex | 6 | 9 |
| 2 | MST | Medial Superior Temporal Area | 3 | 0 |
| 3 | V6 | Sixth Visual Area | 3 | 1 |
| 4 | V2 | Second Visual Area | 6 | 9 |
| 5 | V3 | Third Visual Area | 7 | 7 |
| 6 | V4 | Fourth Visual Area | 6 | 10 |
| 7 | V8 | Eighth Visual Area | 4 | 4 |
| 8 | 4 | Primary Motor Cortex | 6 | 12 |
| 9 | 3b | Primary Sensory Cortex | 2 | 6 |
| 10 | FEF | Frontal Eye Fields | 1 | 4 |
| 11 | PEF | Premotor Eye Fields | 4 | 6 |
| 12 | 55b | Area 55b | 3 | 4 |
| 13 | V3A | Area V3A | 1 | 4 |
| 14 | RSC | RetroSplenial Complex | 2 | 0 |
| 15 | POS2 | Parieto-Occipital Sulcus Area 2 | 4 | 4 |
| 16 | V7 | Seventh Visual | 1 | 3 |
| 17 | IPS1 | Intraparietal Sulcus Area 1 | 2 | 3 |
| 18 | FFC | Fusiform Face Complex | 3 | 3 |
| 19 | V3B | Area V3B | 3 | 4 |
| 20 | LO1 | Area Lateral Occipital 1 | 1 | 1 |
| 21 | LO2 | Area Lateral Occipital 2 | 1 | 0 |
| 22 | PIT | Posterior Inferotemporal Complex | 2 | 2 |
| 23 | MT | Middle Temporal Area | 4 | 0 |
| 24 | A1 | Primary Auditory Cortex | 4 | 4 |
| 25 | PSL | Perisylvian Language Area | 2 | 5 |
| 26 | SFL | Superior Frontal Language Area | 0 | 1 |
| 27 | PCV | Precuneus Visual Area | 2 | 2 |
| 28 | STV | Superior Temporal Visual Area | 2 | 2 |
| 29 | 7Pm | Medial Area 7P | 3 | 3 |
| 30 | 7m | Area 7m | 5 | 3 |
| 31 | POS1 | Parieto-Occipital Sulcus Area 1 | 4 | 2 |
| 32 | 23d | Area 23d | 1 | 0 |
| 33 | v23ab | Area ventral 23 a+b | 1 | 0 |
| 34 | d23ab | Area dorsal 23 a+b | 0 | 0 |

| GLASSER atlas | | | Left | Right |
|---|---|---|---|---|
| 35 | 31pv | Area 31p ventral | 2 | 0 |
| 36 | 5m | Area 5m | 2 | 0 |
| 37 | 5mv | Area 5m ventral | 4 | 1 |
| 38 | 23c | Area 23c | 4 | 0 |
| 39 | 5L | Area 5L | 0 | 1 |
| 40 | 24dd | Dorsal Area 24d | 3 | 0 |
| 41 | 24dv | Ventral Area 24d | 1 | 0 |
| 42 | 7AL | Lateral Area 7A | 2 | 2 |
| 43 | SCEF | Supplementary and Cingulate Eye Field | 1 | 1 |
| 44 | 6ma | Area 6m anterior | 0 | 1 |
| 45 | 7Am | Medial Area 7A | 3 | 2 |
| 46 | 7PL | Lateral Area 7P | 0 | 1 |
| 47 | 7PC | Area 7PC | 3 | 2 |
| 48 | LIPv | Area Letral Intraparietal ventral | 5 | 5 |
| 49 | VIP | Ventral Intraparietal Complex | 3 | 1 |
| 50 | MIP | Medial Intraparietal Area | 2 | 3 |
| 51 | 1 | Area 1 | 3 | 4 |
| 52 | 2 | Area 2 | 5 | 3 |
| 53 | 3a | Area 3a | 3 | 9 |
| 54 | 6d | Dorsal Area 6 | 2 | 3 |
| 55 | 6mp | Area 6mp | 2 | 0 |
| 56 | 6v | Ventral Area 6 | 3 | 6 |
| 57 | p24pr | Area Posterior 24 prime | 1 | 0 |
| 58 | 33pr | Area 33 prime | 1 | 0 |
| 59 | a24pr | Anterior 24 prime | 1 | 0 |
| 60 | p32pr | Area p32 prime | 1 | 0 |
| 61 | a24 | Area 24a | 0 | 0 |
| 62 | d32 | Area dorsal 32 | 0 | 0 |
| 63 | 8BM | Area 8BM | 0 | 0 |
| 64 | p32 | Area p32 | 0 | 0 |
| 65 | 10r | Area 10r | 0 | 0 |
| 66 | 47m | Area 47m | 2 | 1 |
| 67 | 8Av | Area 8Av | 3 | 7 |
| 68 | 8Ad | Area 8Ad | 1 | 0 |
| 69 | 9m | Area 9 Middle | 0 | 0 |
| 70 | 8BL | Area 8B Lateral | 0 | 0 |
| 71 | 9p | Area 9 Posterior | 0 | 0 |
| 72 | 10d | Area 10d | 0 | 0 |
| 73 | 8C | Area 8C | 5 | 6 |

| GLASSER atlas | | | Left | Right |
|---|---|---|---|---|
| 74 | 44 | Area 44 | 4 | 5 |
| 75 | 45 | Area 45 | 4 | 5 |
| 76 | 47l | Area 47l | 4 | 5 |
| 77 | a47r | Area anterior 47r | 2 | 1 |
| 78 | 6r | Rostral Area 6 | 6 | 8 |
| 79 | IFJa | Area IFJa | 4 | 6 |
| 80 | IFJp | Area IFJp | 6 | 6 |
| 81 | IFSp | Area IFSp | 2 | 5 |
| 82 | IFSa | Area IFSa | 2 | 3 |
| 83 | p9-46v | Area posterior 9-46v | 2 | 4 |
| 84 | 46 | Area 46 | 1 | 4 |
| 85 | a9-46v | Area anterior 9-46v | 1 | 2 |
| 86 | 9-46d | Area 9-46d | 1 | 1 |
| 87 | 9a | Area 9 anterior | 0 | 0 |
| 88 | 10v | Area 10v | 0 | 0 |
| 89 | a10p | Area anterior 10p | 0 | 0 |
| 90 | 10pp | Polar 10p | 0 | 0 |
| 91 | 11l | Area 11l | 2 | 1 |
| 92 | 13l | Area 13l | 1 | 2 |
| 93 | OFC | Orbital Frontal Complex | 0 | 0 |
| 94 | 47s | Area 47s | 4 | 3 |
| 95 | LIPd | Area Lateral Intraparietal dorsal | 3 | 3 |
| 96 | 6a | Area 6 anterior | 2 | 5 |
| 97 | i6-8 | Inferior 6-8 Transitional Area | 1 | 5 |
| 98 | s6-8 | Superior 6-8 Transitional Area | 0 | 1 |
| 99 | 43 | Area 43 | 6 | 6 |
| 100 | OP4 | Area OP4/PV | 4 | 4 |
| 101 | OP1 | Area OP1/SII | 5 | 6 |
| 102 | OP2-3 | Area OP2-3/V3 | 6 | 7 |
| 103 | 52 | Area 52 | 5 | 5 |
| 104 | RI | Retroinsular Cortex | 3 | 5 |
| 105 | PFcm | Area PFcm | 8 | 6 |
| 106 | PoI2 | Posterior Insular Area 2 | 8 | 12 |
| 107 | TA2 | Area TA2 | 0 | 6 |
| 108 | FOP4 | Frontal OPercular Area 4 | 6 | 7 |
| 109 | MI | Middle Insular Area | 5 | 8 |
| 110 | Pir | Pirform Cortex | 7 | 6 |
| 111 | AVI | Anterior Ventral Insular Area | 4 | 7 |
| 112 | AAIC | Anterior Agranular Insular Complex | 5 | 6 |

| GLASSER atlas | | | Left | Right |
|---|---|---|---|---|
| 113 | FOP1 | Frontal OPercular Area 1 | 5 | 6 |
| 114 | FOP3 | Frontal OPercular Area 3 | 5 | 8 |
| 115 | FOP2 | Frontal OPercular Area 2 | 4 | 8 |
| 116 | PFt | Area PFt | 3 | 3 |
| 117 | AIP | Anterior Intraparietal Area | 4 | 5 |
| 118 | EC | Enthorhinal Cortex | 1 | 1 |
| 119 | PreS | Presubiculum | 3 | 1 |
| 120 | H | Hippocampus | 4 | 1 |
| 121 | ProS | Prostriate Area | 2 | 1 |
| 122 | PeEc | Perirhinal Ectorhinal Cortex | 0 | 1 |
| 123 | STGa | Area STGa | 2 | 1 |
| 124 | PBelt | ParaBelt Complex | 3 | 6 |
| 125 | A5 | Auditory 5 Complex | 0 | 2 |
| 126 | PHA1 | Parahippocampal Area 1 | 3 | 1 |
| 127 | PHA3 | Parahippocampal Area 3 | 2 | 2 |
| 128 | STSda | Area STSd anterior | 1 | 1 |
| 129 | STSdp | Area STSd posterior | 2 | 2 |
| 130 | STSvp | Area STSv posterior | 1 | 2 |
| 131 | TGd | Area TG dorsal | 2 | 1 |
| 132 | TE1a | Area TE1 anterior | 1 | 1 |
| 133 | TE1p | Area TE1 posterior | 0 | 2 |
| 134 | TE2a | Area TE1 anterior | 1 | 1 |
| 135 | TF | Area TF | 0 | 2 |
| 136 | TE2p | Area TE2 posterior | 1 | 1 |
| 137 | PHT | Area PHT | 3 | 2 |
| 138 | PH | Area PH | 2 | 1 |
| 139 | TPOJ1 | Area Temporoparietooccipital Junction 1 | 2 | 3 |
| 140 | TPOJ2 | Area Temporoparietooccipital Junction 2 | 3 | 1 |
| 141 | TPOJ3 | Area Temporoparietooccipital Junction 3 | 4 | 1 |
| 142 | DVT | Dorsal Transitional Visual Area | 5 | 5 |
| 143 | PGp | Area PGp | 3 | 1 |
| 144 | IP2 | Area Intraparietal 2 | 6 | 4 |
| 145 | IP1 | Area Intraparietal 1 | 3 | 3 |
| 146 | IP0 | Area Intraparietal 0 | 3 | 5 |
| 147 | PFop | Area PF opercular | 6 | 4 |
| 148 | PF | Area PF Complex | 6 | 3 |
| 149 | PFm | Area PFm Complex | 5 | 3 |
| 150 | PGi | Area PGi | 6 | 2 |
| 151 | PGs | Area PGs | 4 | 1 |

| GLASSER atlas | | | Left | Right |
|---|---|---|---|---|
| 152 | V6A | AreaV6A | 0 | 1 |
| 153 | VMV1 | Ventromedial Visual Area 1 | 2 | 1 |
| 154 | VMV3 | Ventromedial Visual Area 3 | 2 | 1 |
| 155 | PHA2 | Parahippocampal Area 2 | 2 | 1 |
| 156 | V4t | Area V4t | 3 | 0 |
| 157 | FST | Area FST | 3 | 1 |
| 158 | V3CD | Area V3CD | 3 | 3 |
| 159 | LO3 | Area Lateral Occipital 3 | 4 | 0 |
| 160 | VMV2 | Ventromedial Visual Area 2 | 2 | 1 |
| 161 | 31pd | Area 31pd | 3 | 1 |
| 162 | 31a | Area 31a | 0 | 0 |
| 163 | VVC | Ventral Visual Complex | 2 | 3 |
| 164 | 25 | Area 25 | 0 | 0 |
| 165 | s32 | Area s32 | 0 | 0 |
| 166 | pOFC | Posterior OFC Complex | 1 | 1 |
| 167 | PoI1 | Area Posterior Insular 1 | 7 | 9 |
| 168 | Ig | Insular Granular Complex | 6 | 9 |
| 169 | FOP5 | Area Frontal Opercular 5 | 4 | 5 |
| 170 | p10p | Area posterior 10p | 0 | 0 |
| 171 | p47r | Area posterior 47r | 1 | 2 |
| 172 | TGv | Area TG ventral | 1 | 1 |
| 173 | MBelt | Medial Belt Complex | 1 | 7 |
| 174 | LBelt | Lateral Belt Complex | 4 | 4 |
| 175 | A4 | Auditory 4 Complex | 3 | 4 |
| 176 | STSva | Area STSv anterior | 2 | 1 |
| 177 | TE1m | Area TE1 Middle | 0 | 1 |
| 178 | PI | Para-Insular Area | 2 | 5 |
| 179 | a32pr | Area anterior 32 prime | 0 | 0 |
| 180 | p24 | Area posterior 24 | 0 | 0 |

| CAT atlas | | Left | Right |
|---|---|---|---|
| 1 | Anterior Commissure | 5 | 7 |
| 2 | Anterior Segment Arcuate Fasciculus | 13 | 14 |
| 3 | Long Segment Arcuate Fasciculus | 14 | 8 |
| 4 | Posterior Segment Arcuate Fasciculus | 12 | 6 |
| 5 | Cingulum | 14 | 16 |
| 6 | Corpus Callosum | 28 | 34 |
| 7 | Corticoponto Cerebellum | 21 | 19 |
| 8 | Corticospinal Tract | 32 | 27 |
| 9 | Fornix | 7 | 6 |
| 10 | Inferior Cerebellar Pedunculus | 1 | 3 |
| 11 | Inferior Longitudinal Fasciculus | 16 | 11 |
| 12 | Inferior Occipitofrontal Fasciculus | 15 | 21 |
| 13 | Internal Capsule | 30 | 28 |
| 14 | Optic Radiations | 18 | 13 |
| 15 | Superior Cerebelar Pedunculus | 0 | 2 |
| 16 | Uncinate | 9 | 10 |

## Supplementary materials chapter 4

**S1.** Model specifications
**S2.** List of number of participants per ROI

## References

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Consequence of stroke for feature recall and binding
in visual working memory

## Supplementary material

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## 1   Data analysis

We denote the report feature values of the $N$ sample items in trial $i$ as $\{\theta_1^{(i)}, \ldots, \theta_N^{(i)}\}$, with $\theta_1^{(i)}$ being the target feature value, and we denote the response feature value as $\theta_r^{(i)}$. The response errors are then determined as

$$\epsilon^{(i)} = D_\circ(\theta_r^{(i)}, \theta_1^{(i)}), \tag{1}$$

and the non-target deviations as

$$\tilde{\epsilon}_j^{(i)} = D_\circ(\theta_r^{(i)}, \theta_j^{(i)}) \quad \text{for} \quad j = 2, \ldots, N, \tag{2}$$

where $D_\circ$ is the signed distance on the circle.

The occurrence of swap errors can be visualized by plotting the histogram of non-target deviations, with a central peak indicating that responses are clustered around the report feature values of non-target items. However, if there is a minimum distance between the feature values of all sample items within a trial (as is the case in the present experiment), the distribution of non-target deviations cannot be assumed to be uniform in the absence of swap errors. If the response values are concentrated around the target value, they will tend to be at least that minimum distance away from the report values of the non-target items, resulting in a central dip in the distribution of non-target deviations which may mask any central peak produced by swap errors.

We therefore correct the histogram of non-target deviations by subtracting the expected histogram in the absence of any swap errors (Schneegans and Bays, 2017), computed separately for each participant and each task condition. We determine the deviation of all non-target features from the target feature in each trial,

$$\delta_j^{(i)} = D_\circ(\theta_j^{(i)}, \theta_1^{(i)}) \quad \text{for} \quad j = 2, \ldots, N, \tag{3}$$

and then compute the histogram over all differences

$$\zeta_j^{(i,i')} = D_\circ(\epsilon^{(i)}, \delta_j^{(i')}) \quad \text{for} \quad j = 2, \ldots, N \quad \text{and} \quad i, i' = 1, \ldots, T, \tag{4}$$

where $T$ is the number of trials in each condition. This yields the expected histogram of non-target deviations by shuffling the deviations of responses from targets and the relative position of non-targets to targets across trials.

To test for the presence of swap errors, we determined for each participant the arithmetic mean of the absolute non-target deviations, $|\tilde{\epsilon}_j^{(i)}|$, across all non-targets and trials, and the mean of all shuffled absolute non-target deviations, $|\zeta_j^{(i,i')}|$, and compared these using a paired-samples t-test.

## 2   Neural binding model

### 2.1   Conjunctive population code

We assume that the colors and locations of the sample stimuli are encoded in an idealized conjunctive population code, in which each neuron's activity is determined by its tuning functions for stimulus color and location. Recall is modeled as decoding of memorized features from noisy neural activity. We will describe this neural population model in terms of cue and report feature values. Either role can be taken by color or location, depending on task condition.

The firing rate of neuron $k$ encoding cue feature $\psi_j$ and report feature $\theta_j$ of item $j$ in the sample display is given as

$$\bar{r}_{k,j}(\psi_j, \theta_j) = \frac{\gamma}{NM} \phi_\circ(\psi_j; \psi'_k, \kappa_\psi) \phi_\circ(\theta_j; \theta'_k, \kappa_\theta) \quad (5)$$

Here, $\gamma$ is the mean total firing rate of the population, which is divided by the number of sample items, $N$, and the number of neurons, $M$, that contribute to the encoding of each item. The feature tuning of the neuron is described by von Mises functions with preferred values $\psi'_k$ and $\theta'_k$ for cue and report feature, respectively, and associated concentration parameters $\kappa_\psi$ and $\kappa_\theta$. We assume that the shape of the tuning curves is fixed throughout the population, and individual neurons only differ in their preferred feature values, which uniformly sample the underlying feature space of color-location combinations.

Discrete spikes are produced based on each neuron's firing rate via independent Poisson processes,

$$r_{k,j} \sim \text{Pois}(\bar{r}_{k,j}) \quad (6)$$

Due to the superposition property of the Poisson distribution, the total number of spikes, $n_j$, that contribute to representing the features of each item $j$ is then likewise a Poisson random variable,

$$n_j \sim \text{Pois}\left(\frac{\gamma}{N}\right). \quad (7)$$

## 2.2 Response probabilities

Feature recall is modeled as maximum likelihood estimation of the encoded feature values from the noisy spiking activity over a fixed time window. To determine the distribution of decoding errors, we deviate from the method used by Schneegans and Bays (2017), and instead build on new results from Schneegans et al. (2019) to derive a more elegant solution. In this publication it has been shown that for a given number of spikes contributing to the encoding of item $j$, the distribution of decoded values $\hat{\theta}_j$ can be closely approximated by a von Mises distribution around the true feature value $\theta_j$ in each feature dimension, with precision scaled by the number of spikes $n_j$:

$$p_{\text{dec}}\left(\hat{\theta}_j \mid \theta_j, n_j\right) = \phi_\circ\left(\hat{\theta}_j; \theta_j, \kappa(n_j\omega_\theta)\right) \quad (8)$$

Here, $\omega_\theta$ is the precision (as Fisher information) corresponding to the tuning curve concentration $\kappa_\theta$, which is determined as $\omega = \kappa \frac{I_1(\kappa)}{I_0(\kappa)}$, and the term

$\kappa(n_j\omega_\theta)$ describes the concentration parameter yielding a multiple of the base precision $\omega_\theta$, which can be obtained by numerical inversion of the same relationship.

The joint distribution of decoded cue and report feature values can then be described as

$$p_{\text{dec}}\left(\hat{\theta}_j, \hat{\psi}_j \mid \theta_j, \psi_j\right)$$
$$= \sum_{n_j=0}^{\infty} \text{Pr}_{\text{Pois}}\left(n_j, \frac{\gamma}{N}\right) p_{\text{dec}}\left(\hat{\theta}_j \mid \theta_j, n_j\right) p_{\text{dec}}\left(\hat{\psi}_j \mid \psi_j, n_j\right) \quad (9)$$

It should be noted that decoding errors in the two feature dimensions are not independent of each other, since both depend on the number of spikes in the neural population that contribute to decoding the item's features.

We assume that the cue and response features of all items are decoded from the neural activity when a cue is given. The item whose decoded cue feature value is closest to the actual cue is selected for response generation, and its decoded report feature value is produced as response. The probability that a certain report feature value $\theta_r$ is chosen as a response in a trial with item report and cue feature values $\boldsymbol{\theta}$ and $\boldsymbol{\psi}$, respectively, is then

$$p_{\text{resp}}\left(\theta_r \mid \boldsymbol{\theta}, \boldsymbol{\psi}\right) = \sum_{j=1}^{N} p\left(\hat{\theta}_j = \theta_r \wedge \text{item } j \text{ selected} \mid \boldsymbol{\theta}, \boldsymbol{\psi}\right). \quad (10)$$

The probability that an item is selected for response generation is determined by its decoded cue feature, and due to the aforementioned dependence between decoding errors it is not independent from the obtained report feature value. But we can separate these probabilities by conditioning on the number of available spikes, $n_j$:

$$p_{\text{resp}}\left(\theta_r \mid \boldsymbol{\theta}, \boldsymbol{\psi}\right)$$
$$= \sum_{j=1}^{N} \sum_{n_j=0}^{\infty} \text{Pr}_{\text{Pois}}\left(n_j, \frac{\gamma}{N}\right) p_{\text{dec}}\left(\theta_r \mid \theta_j, n_j\right) \text{Pr}_{\text{sel}}\left(j \mid \boldsymbol{\psi}, n_j\right) \quad (11)$$

The conditional probability of decoding a certain report feature value given the spike count and true feature value in this equation can be determined as in Eq. 8.

The probability that an item is selected (i.e., its decoded cue feature value is closest to the actual cue) can be computed by numerical integration

as

$$\mathrm{Pr}_{\mathrm{sel}}\left(j \mid \boldsymbol{\psi}, n_j\right)$$
$$= \int_0^\pi p\left(D_\circ(\hat{\psi}_j - \psi_c) = s \,\Big|\, \psi_j, n_j\right) \prod_{j' \neq j} p\left(D_\circ(\hat{\psi}_{j'} - \psi_c) > s \,\Big|\, \psi_{j'}\right) ds,$$
$$(12)$$

where $\psi_c$ is the feature value of the actually given cue. The first probability term in this integral can be evaluated based on Eq. 8, while the second term requires marginalizing over the possible sample counts,

$$p_{\mathrm{dec}}\left(\hat{\psi}_{j'} \,\Big|\, \psi_{j'}\right) = \sum_{n_{j'}=0}^\infty \mathrm{Pr}_{\mathrm{Pois}}\left(n_{j'}, \frac{\gamma}{N}\right) p_{\mathrm{dec}}\left(\hat{\psi}_{j'} \,\Big|\, \psi_{j'}, n_{j'}\right). \qquad (13)$$

## 2.3 Binding and reporting deficits

In order to detect specific impairments in feature binding performance, we extend the model in a way which relaxes the assumption that memory precision for a feature when used as a cue from is the same as memory precision for the same feature when it is reported. More specifically, we allow the number of spikes that contribute to the selection of the cued item to be different from the number of spikes that contribute to decoding of the report features. This is compatible with the idea that the pool of neurons underlying memory for individual features may be separate from the one underlying binding memory, without making any strong assumptions about the specific neural architecture.

We introduce a new parameter $a_{\mathrm{select}}$ that specifies the mean proportion of total spikes $n_j$ that are available for selecting an item for response based on the cue. We assume that this adjusted number of spikes $\tilde{n}_j$ is drawn from a binomial distribution with success rate $a_{\mathrm{select}}$, such that the selection probability used in Eq. 11 is now given as

$$\mathrm{Pr}_{\mathrm{sel}}\left(j \mid \boldsymbol{\psi}, n_j, a_{\mathrm{select}}\right) = \sum_{\tilde{n}_j=0}^{n_j} \mathrm{Pr}_{\mathrm{Binom}}(\tilde{n}_j; n_j, a_{\mathrm{select}}) \,\mathrm{Pr}_{\mathrm{sel}}\left(j \mid \boldsymbol{\psi}, \tilde{n}_j\right), \quad (14)$$

where $\mathrm{Pr}_{\mathrm{sel}}\left(j \mid \boldsymbol{\psi}, \tilde{n}_j\right)$ is again determined as in Eq. 12.

We also allow for the converse effect, i.e. an impairment of reporting the feature value after an item has been selected. For this case, we assume that the number of spikes for decoding the report feature is a subset of the total

spikes, likewise drawn from a binomial distribution with success rate $a_{\mathrm{report}}$. The decoding probability of the report in Eq. 11 is then computed as

$$p_{\mathrm{dec}}\left(\theta \mid \theta_j, n_j, a_{\mathrm{report}}\right) = \sum_{\tilde{n}_j=0}^{n_j} \mathrm{Pr}_{\mathrm{Binom}}(\tilde{n}_j; n_j, a_{\mathrm{report}}) p_{\mathrm{dec}}\left(\theta \mid \theta_j, \tilde{n}_j\right), \quad (15)$$

with $p_{\mathrm{dec}}\left(\theta \mid \theta_j, \tilde{n}_j\right)$ determined as in Eq. 8.

We combine the model variants with binding deficit and reporting deficit into a single model with a *binding index b* as free parameter, in such a way that $b = 0$ reflects no binding or reporting deficit (all spikes are available both for selecting the report item and decoding its report feature value), $b = -1$ indicates complete loss of binding memory (no spikes available for selecting the report item, so each sample item is selected with equal probability) and $b = 1$ indicates complete loss of feature reporting ability (no spikes available for decoding the report feature value, so all responses are drawn from a uniform distribution):

$$\begin{aligned} a_{\mathrm{select}} = 1 + b, \ a_{\mathrm{report}} = 1 \quad &\text{if } b \leq 0 \\ a_{\mathrm{select}} = 1, \ a_{\mathrm{report}} = 1 - b \quad &\text{otherwise} \end{aligned} \qquad (16)$$

## 2.4 Priors for model parameters

Due to the very limited amount of behavioral data collected for each participant, some aspects of the model fits can be underconstrained in the current study. The first of these concerns a trade-off between the mean total spike rate $\gamma$ and the tuning curve concentrations $\kappa_\theta$ and $\kappa_\psi$. An increase in recall precision can be achieved in the model either by increasing the spike rate or the concentration parameters. In most VWM studies, recall performance is measured at different set sizes. The neural population model assumes that the total spike rate is distributed among all sample items, while the tuning curves remain fixed across set sizes. This mechanism has been shown to successfully account for set size effects (Bays, 2014), and provides sufficient constraints to obtain robust estimates for each parameter.

In the present study with a single set size and small number of trials, we employ a weakly informative prior on the parameter $\gamma$. The prior is based on population model fits to a database of delayed reproduction tasks with color report (Schneegans et al., 2019), but with increased variability to avoid overly constraining the model fits. It is implemented as a Gamma distribution,

$$p(\gamma) = \frac{1}{\Gamma(k)\theta^k} \gamma^{k-1} e^{\frac{\gamma}{\theta}}, \qquad (17)$$

with shape parameter $k = 2$ and scale parameter $\theta = 8$. This prior penalizes extremely small values of $\gamma$ as well as very large values. In particular it prevents $\gamma$ from going towards infinity in the model fits (while the $\kappa$ values go towards zero), which otherwise happens for a few participants, without substantially altering the resulting error distributions.

Another issue that arises in fitting the model to the data is that some participants do not show any identifiable swap errors, due to the small number of trials and the relatively low difficulty of the task. In these participants, increasing the precision for the cue feature towards infinity improves the quality of fit in each condition. To avoid unrealistically high estimates of cue feature precision, we add a weakly informative prior on the probability of swap errors. This prior is implemented by computing for a given set of model parameters the probability that a swap error occurs if both non-target items have the minimum allowed distance $(30°)$ to the target in the cue dimension, using Eq. 12. Then a Beta-distribution distribution is applied to this probablity $p_{\text{NT}}$,

$$p(p_{\text{NT}}) = \frac{p_{\text{NT}}^{\alpha-1}(1-p_{\text{NT}})^{\beta-1}}{B(\alpha,\beta)} \qquad (18)$$

with $\alpha = \beta = 2$. This prior is directly equivalent to adding two trials with minimum distance between cue features to each participant's data in each condition, one of which results in a swap error and the other in a target response (while ignoring the actually reported feature), and it penalizes both very small and very high (close to one) swap probabilities.

## 2.5   Model fitting and comparison

We determined maximum likelihood fits of each model to the behavioral data of each participant. For the neural binding model, we obtained both separate fits for each task condition (six parameters in total), and a combined fit with shared parameters across both condition (parameters $\gamma$, $\kappa_{\text{color}}$ and $\kappa_{\text{location}}$, with the latter assigned either to the cue or the report dimension according to task condition). The model with additional binding index, $b$, was fit to the combined data only (four parameters in total). Maximum likelihood fits were determined via the Nelder-Mead simplex method (function `fminsearch` in Matlab), using a grid of possible initial values for all parameters. Initial values were $[6, 12, 24]$ for $\gamma$, $[2, 5, 12]$ for $\kappa$ in each feature dimension, and $[-0.3, 0, 0.3]$ for $b$.

We compare models' quality of fit using the Akaike information criterion

with correction for small sample size (AICc),

$$AICc = 2k - 2\ln L + \frac{2k^2 + 2k}{n - k - 1}, \qquad (19)$$

where $k$ is the total number of free parameters in each model, $L$ is the likelihood of the fitted model, and $n$ is the total number of trials for each participant.

The pattern of results would not qualitatively change if we used the Bayesian information criterion instead of the AICc for model comparisons, although the combined fit of both task conditions with the original neural binding model (which has the lowest number of free parameters) would have an even larger advantage over the alternative models.

## 2.6   Model-based performance measures

We use the circular standard deviation of the decoding errors in the absence of binding or reporting deficits as a measure of memory performance. To this end, we compute the probability distribution $p_{dec}(\hat{\theta} \,|\, \theta)$ as in Eq. 13, and numerically determine its circular standard deviation. This measure incorporates the concentration parameters of the tuning curves in each feature dimension, $\kappa_{\text{location}}$ and $\kappa_{\text{color}}$, as well as the shared spike rate parameter $\gamma$. Due to the possible trade-off between these parameters described above, we do not analyze and compare these individual parameters directly. Additionally, we use the binding index estimated for each participant as measure of specific binding or reporting deficits.

We can also estimate the proportion of swap errors that occur for each participant from the model fits. For a single trial, the posterior probability that the given response $\theta_r$ was the result of selecting item $j$ for response generation can be derived from Eq. 11 as

$$\Pr(j \,|\, \theta_r, \boldsymbol{\theta}, \boldsymbol{\psi}) = \frac{\sum_{n_j=0}^{\infty} \Pr_{\text{Pois}}\left(n_j, \frac{\gamma}{N}\right) p_{\text{dec}}\left(\theta_r \,|\, \theta_j, n_j\right) \Pr_{\text{sel}}\left(j \,|\, \boldsymbol{\psi}, n_j\right)}{p_{\text{resp}}\left(\theta_r \,|\, \boldsymbol{\theta}, \boldsymbol{\psi}\right)}. \qquad (20)$$

To estimate the overall proportion of swap errors, we sum the probability values obtained from this equation for the two non-target items in each trial, and average the sum over all trials.

# Supplementary tables

**Table S1. Number of participants per region of interest.** Shaded areas were included in the atlas-based LSM analysis. Only the areas in a dark shade of grey were signicantly associated with one of the outcome measures. The number of subjects indicates how many subjects had a lesion in each area.

| Brodmann areas | | *N* subjects |
|---|---|---|
| 1\|1_L | primary somatosensory cortex | 3 |
| 2\|1_R | primary somatosensory cortex | 2 |
| 3\|2_L | primary somatosensory cortex | 3 |
| 4\|2_R | primary somatosensory cortex | 4 |
| 5\|3_L | primary somatosensory cortex | 7 |
| 6\|3_R | primary somatosensory cortex | 5 |
| 7\|4_L | primary motor cortex | 8 |
| 8\|4_R | primary motor cortex | 5 |
| 9\|5_L | somatosensory association cortex | 2 |
| 10\|5_R | somatosensory association cortex | 3 |
| 11\|6_L | premotor cortex and supplementary motor cortex | 15 |
| 12\|6_R | premotor cortex and supplementary motor cortex | 11 |
| 13\|7_L | superior parietal lobe | 4 |
| 14\|7_R | superior parietal lobe | 5 |
| 15\|8_L | frontal eyefield | 2 |
| 16\|8_R | frontal eyefield | 3 |
| 17\|9_L | dorsolateral prefrontal cortex | 2 |
| 18\|9_R | dorsolateral prefrontal cortex | 3 |
| 19\|10_L | anterior prefrontal cortex | 1 |
| 20\|10_R | anterior prefrontal cortex | 1 |
| 21\|11_L | orbitofrontal | 2 |
| 22\|11_R | orbitofrontal | 3 |
| 23\|17_L | V1 | 6 |
| 24\|17_R | V1 | 8 |
| 25\|18_L | V2 | 7 |
| 26\|18_R | V2 | 10 |
| 27\|19_L | V3,4,5 | 10 |
| 28\|19_R | V3,4,5 | 12 |
| 29\|20_L | inferior temporal gyrus | 3 |
| 30\|20_R | inferior temporal gyrus | 4 |
| 31\|21_L | middle temporal gyrus | 4 |
| 32\|21_R | middle temporal gyrus | 4 |

| Brodmann areas | | *N* subjects |
|---|---|---|
| 32\|21_R | middle temporal gyrus | 4 |
| 33\|22_L | superior temporal gyrus | 3 |
| 34\|22_R | superior temporal gyrus | 5 |
| 35\|23_L | cingulate cortex | 2 |
| 36\|23_R | cingulate cortex | 2 |
| 37\|24_L | cingulate cortex | 1 |
| 38\|24_R | cingulate cortex | 1 |
| 39\|25_L | subgenual area | 0 |
| 40\|25_R | subgenual area | 2 |
| 41\|26_L | retrosplenial region | 0 |
| 42\|26_R | retrosplenial region | 0 |
| 43\|27_L | piriform cortex | 0 |
| 44\|27_R | piriform cortex | 2 |
| 45\|28_L | cingulate cortex | 0 |
| 46\|28_R | cingulate cortex | 1 |
| 47\|29_L | cingulate cortex | 0 |
| 48\|29_R | cingulate cortex | 0 |
| 49\|30_L | cingulate cortex | 1 |
| 50\|30_R | cingulate cortex | 4 |
| 51\|32_L | cingulate cortex | 0 |
| 52\|32_R | cingulate cortex | 2 |
| 53\|34_L | dorsal enthorihinal cortex | 2 |
| 54\|34_R | dorsal enthorihinal cortex | 2 |
| 55\|35_L | perirhinal cortex | 1 |
| 56\|35_R | perirhinal cortex | 2 |
| 57\|36_L | perirhinal cortex | 0 |
| 58\|36_R | perirhinal cortex | 1 |
| 59\|37_L | fusiform gyrus | 6 |
| 60\|37_R | fusiform gyrus | 9 |
| 61\|38_L | temporal pole | 3 |
| 62\|38_R | temporal pole | 4 |
| 63\|39_L | angular gyrus | 3 |
| 64\|39_R | angular gyrus | 3 |
| 65\|40_L | supramarginal gyrus | 3 |
| 66\|40_R | supramarginal gyrus | 5 |
| 67\|41_L | primary auditory cortex / heschl gyrus | 5 |
| 68\|41_R | primary auditory cortex / heschl gyrus | 3 |
| 69\|42_L | primary auditory cortex / heschl gyrus | 2 |
| 70\|42_R | primary auditory cortex / heschl gyrus | 4 |

| Brodmann areas | | *N* subjects |
|---|---|---|
| 71\|43_L | primary gustatory cortex | 6 |
| 72\|43_R | primary gustatory cortex | 4 |
| 73\|44_L | broca | 10 |
| 74\|44_R | broca | 9 |
| 75\|45_L | broca | 4 |
| 76\|45_R | broca | 5 |
| 77\|46_L | dorsolateral prefrontal cortex | 3 |
| 78\|46_R | dorsolateral prefrontal cortex | 5 |
| 79\|47_L | inferior frontal gyrus | 4 |
| 80\|47_R | inferior frontal gyrus | 6 |
| 81\|48_L | retrosubicular area | 25 |
| 82\|48_R | retrosubicular area | 18 |

| CAT atlas | *N* subjects |
|---|---|
| 1\| Anterior commissure left | 2 |
| 2\| Arcuate anterior segment left | 11 |
| 3\| Longs segment left | 13 |
| 4\| Arcuate posterior segment left | 6 |
| 5\| Cingulum left | 9 |
| 6\| Corpus callosum left | 19 |
| 7\| Cortico-ponto cerebellum left | 20 |
| 8\| Cortico-spinal left | 27 |
| 9\| Fornix left | 3 |
| 10\| Inferior cerebellar pedunculus left | 4 |
| 11\| Inferior longitudinal fasciculus left | 11 |
| 12\| Inferior occipito-frontal fasciculus left | 11 |
| 13\| Internal capsule left | 25 |
| 14\| Optic radiations left | 13 |
| 15\| Superior cerebelar pedunculus left | 2 |
| 16\| Uncinate left | 7 |
| 17\| Anterior commissure right | 5 |
| 18\| Arcuate anterior segment right | 9 |
| 19\| Long segment right | 6 |
| 20\| Arcuate posterior segment right | 5 |
| 21\| Cingulum right | 9 |
| 22\| Corpus callosum right | 21 |
| 23\| Cortico-ponto cerebellum right | 13 |
| 24\| Cortico-spinal right | 18 |
| 25\| Fornix right | 5 |

| CAT atlas | *N* subjects |
|---|---|
| 26\| Inferior cerebellar pedunculus right | 2 |
| 27\| Inferior longitudinal fasciculus right | 11 |
| 28\| Inferior occipito-frontal fasciculus right | 18 |
| 29\| Internal capsule right | 21 |
| 30\| Optic radiations right | 7 |
| 31\| Superior cerebelar pedunculus right | 2 |
| 32\| Uncinate right | 9 |

**Note.** Shaded areas were included in the atlas-based LSM analysis. Only the areas in a dark shade of grey were significantly associated with one of the outcome measures. The number of subjects shows how many subjects has a lesion in that area.

# References

Bays, P. M. (2014). Noise in neural populations accounts for errors in working memory. Journal of Neuroscience, 34(10):3632-3645.

Schneegans, S. and Bays, P. M. (2017). Neural architecture for feature binding in visual working memory. Journal of Neuroscience, 37(14):3913-3925.

Schneegans, S., Taylor, R., and Bays, P. M. (2019). Stochastic sampling provides a unifying account of working memory limits. BioRxiv, page 771071.

# Supplementary materials chapter 5

**Fig. 3.** Performance on low-load tasks categorized by modality (verbal and non-verbal)
**Fig. 4.** Performance on high-load tasks categorized by modality (verbal and non-verbal)
**Fig. 5.** Overall working memory performance categorized by interval between stroke
and assessment (sub-acute < 3 months and chronic)

**Appendix A** PRISMA Checklist
**Appendix B** Adapted RTI Item Bank for Assessing Risk of Bias and Confounding

**S1.** Overview of articles included
**S2.** RTI items rated for all studies
**S3.** Additional results: sub-analyses



**Fig. 3.** Performance on low-load tasks categorized by modality (verbal and non-verbal)

| Study | Hedges' g | 95% CI | |
|---|---|---|---|
| Andrews et al., 2013 | −0.33 | −0.7 | 0.04 |
| Baldo et al., 2006 | −1.47 | −2.34 | −0.6 |
| Beeson et al., 1993 | −0.27 | −0.89 | 0.35 |
| Cao et al., 2007 | −0.31 | −0.74 | 0.13 |
| Grosdemange et al., 2015 | 0.37 | −0.11 | 0.85 |
| Kant et al., 2014 | −0.53 | −0.95 | −0.11 |
| Kessels et al., 2002 | −0.66 | −1.08 | −0.24 |
| Liebermann et al., 2013 | −0.67 | −1.3 | −0.03 |
| Luukkainen–Markkula et al., 2011 | −2.22 | −3.24 | −1.21 |
| Pergola et al., 2012 | −1.92 | −2.62 | −1.21 |
| Piccardi et al., 2016 | −0.33 | −0.49 | −0.17 |
| Ramsey et al., 2017 | −0.53 | −0.81 | −0.24 |
| Ravizza et al., 2005 | −0.12 | −0.89 | 0.66 |
| Rousseaux et al., 2008 | 0 | −0.61 | 0.61 |
| Roussel et al., 2012 | −0.65 | −0.11 | 0.21 |
| Schweinberger et al., 1992 | −0.19 | −0.69 | 0.31 |
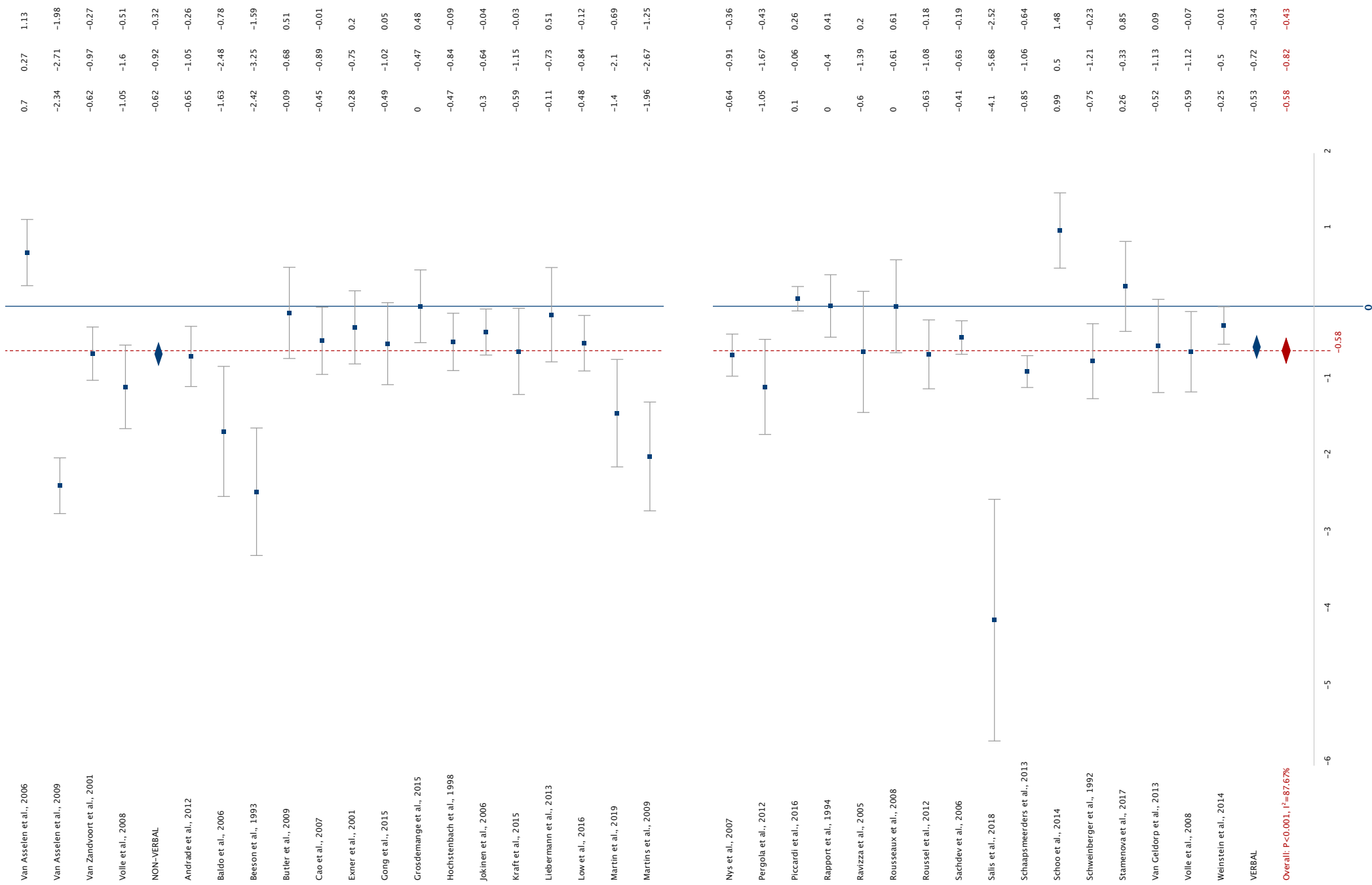
**Fig. 3.** Continued

**Fig. 4.** Performance on high-load tasks categorized by modality (verbal and non-verbal)

**Fig. 4.** Continued



| | | | |
|---|---|---|---|
| Schoo et al., 2014 | 0 | -0.46 | 0.46 |
| Schweinberger et al., 1992 | -0.69 | -1.21 | -0.17 |
| Snaphaan et al., 2009 | -0.4 | -0.95 | 0.16 |
| Stamenova et al., 2017 | -0.02 | -0.61 | 0.56 |
| Su et al., 2018 | -0.57 | -0.97 | -0.18 |
| Van Asselen et al., 2006 | -1.44 | -1.92 | -0.95 |
| Van Geldorp et al., 2013 | -0.55 | -1.16 | 0.06 |
| Volle et al., 2008 | -0.8 | -1.34 | -0.27 |
| Weinstein et al., 2014 | -0.56 | -0.82 | 0.31 |
| VERBAL | -0.63 | -0.83 | -0.44 |
| Overall: P<0.001, I²=76.71% | -0.59 | -0.73 | -0.45 |

**Fig. 5.** Overall working memory performance categorized by interval between stroke and assessment (sub-acute < 3 months and chronic)



| | Hedges'g | 95%IC | |
|---|---|---|---|
| Gong et al., 2015 | -0.4 | -0.93 | 0.13 |
| Grosdemange et al., 2015 | 0 | 0.14 | -0.34 |
| Jokinen et al., 2006 | -0.43 | -0.77 | -0.09 |
| Kokubo et al., 2015 | -1.83 | -2.67 | -1 |
| Li et al., 2013 | -0.21 | -0.81 | 0.38 |
| Martin et al. 2019 | -1.4 | -2.1 | -0.69 |
| Nys et al. 2007 | -0.67 | -0.94 | -0.39 |
| Rosemann et al., 2017 | 0 | -0.49 | -1.11 |
| Rousseaux et al. 2008 | 0.12 | -0.49 | 0.72 |
| Roussel et al. 2012 | -0.62 | -1.07 | -0.17 |
| Schoo et al. 2014 | 0.5 | 0.02 | 0.97 |
| Snaphaan et al., 2009 | -0.4 | -0.95 | 0.16 |
| Su et al., 2018 | -0.57 | -0.97 | -0.18 |
| Van Zandvoort et al., 2001 | -0.34 | -0.82 | -0.19 |
| SUB-ACUTE | -0.43 | -0.68 | -0.19 |
| Andrade et al. 2012 | -0.57 | -0.96 | -0.18 |

**Fig. 5.** Continued

| Study | | | |
|---|---|---|---|
| Andrews et al., 2013 | -0.53 | -0.91 | -0.16 |
| Andrews et al., 2014 | -0.74 | -1.13 | -0.36 |
| Baldo et al., 2006 | -1.68 | -2.55 | 0.82 |
| Cao et al., 2007 | -0.39 | -0.83 | 0.05 |
| Exner et al., 2001 | -0.28 | -0.75 | 0.2 |
| Kant et al., 2014 | -0.74 | -1.17 | -0.31 |
| Kessels et al., 2002 | -0.66 | -1.08 | -0.24 |
| Martins et al., 2009 | -2.03 | -2.75 | -1.31 |
| Pergola et al., 2012 | -1.85 | -2.59 | -1.11 |
| Rochat et al., 2013 | -0.79 | -1.37 | -0.21 |
| Sachdev et al., 2006 | -0.41 | -0.63 | -0.19 |
| Saldert et al., 2007 | -1.01 | -1.55 | -0.46 |
| Salis et al., 2018 | -0.41 | -6.68 | -2.52 |
| Schaapsmeerders et al., 2013 | -0.85 | -1.06 | -0.64 |
| Stamenova et al., 2017 | 0.12 | -0.47 | 0.71 |
| Van Asselen et al., 2009 | -0.41 | -0.88 | 0.05 |
| Van Asselen et al., 2009 | -2.34 | -2.71 | -1.98 |
| Van Geldorp et al., 2013 | -0.53 | -1.14 | 0.08 |
| Van Zandvoort et al., 2001 | -0.92 | -1.42 | -0.42 |
| Weinstein et al., 2014 | -0.41 | -0.66 | -0.16 |
| | | | |
| CHRONIC | -0.9 | -1.15 | -0.65 |

x-axis: -6  -5  -4  -3  -2  -1  0  1  2

# Appendix A
## PRISMA Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | Title page |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 1 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 2-4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 4 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | N/A |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 5, 6 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 5-8 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 5 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | Fig 1 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 5-8 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 6-7 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 7 and Appendix B |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 7, 8 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis. | 8 |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | Table S2 supplemental materials |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 8 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 9, Fig. 1 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 9-10, Table S1 supplemental materials |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 11 and Table S2 supplemental materials |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 12-13, Table 1, Fig. 3-5 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | Table 1 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 11 and Fig. 2 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 12, 13, Fig. 3-5, Table S3a,b supplemental materials |

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 16-19 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 18, 19 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 16-19 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | Title page and 19 |

**Chapter 5 - Appendix B**

**Adapted RTI Item Bank for Assessing Risk of Bias and Confounding**

Q1. Are inclusion and exclusion criteria applied uniformly?

*Consider patients vs. controls if applicable, otherwise individual patients.*

Q2. Is the recruitment strategy the same across individuals or study groups?

*Consider patients vs. controls if applicable, otherwise individual patients.*

Q3. Is the selection of the comparison group adequate?

*Age and education matched.*

Q5. Is the outcome assessor blinded to exposure status?

*Assessor of cognitive function blinded for clinical status (stroke or not)?*

Q6. Are valid and reliable measures implemented?

*Reliable and conventional ascertainment of stroke?*

Q7. Is the length of follow-up the same across individuals or study groups?

*Delay from stroke to cognitive testing uniform for all individuals?*

Q8. Is the impact of loss to follow-up assessed?

Only applicable if follow-up study.

Q9. Are important primary outcomes reported?

*Cognitive impairment*

*Timing of cognitive testing*

Q13. Are important confounding variables taken into account in the design and/or analysis?

*Stratified by level of importance:*

1. *Age, level of education, prior stroke, pre-existing dementia.*

2. *Vascular risk factors, vascular brain damage, concurrent neuropsychiatric disturbances.*

Q4, Q10, Q11, Q12 of the RTI item bank are not relevant to the included studies.

## Chapter 5 - Online Supplemental Materials

**Table S1** Overview of articles included.

| Study | Patients N subgroups/ specific incl. | Stroke type | Age M (SD) or Median [range] | Interval¹ in months M (SD) [range] | Prior stroke | Prior dementia | Healthy controls | Low-/ high-load | Task | Hedges's g, Variance |
|---|---|---|---|---|---|---|---|---|---|---|
| Andrade et al., 2012* | 50 subcortical | IS | 66.0 (8.9) | > 3 | NS | NS | 50 | both | DSF, DSB | -.57 .04 |
| Andrews et al., 2013* | 14 frontal, 30 non-frontal | NS | 64.4 (12.0) | 88 (60) | NS | NS | 41 | both | 1-, 2-, 3-back | -.48 .04 |
| Andrews et al., 2014* | 21 LH, 20 RH | NS | 65.1 (12.1) | 87 (61) | NS | NS | 41 | high | Letter-Number Sequencing | -.74 .04 |
| Baier et al., 2014 | 8 LH, 21 RH | IS | Median 56 [20-81] | < .5 | NS | NS | 10 | low | Experimental visuospatial task | NA |
| Baldo et al., 2006* | 10 left IPC, 8 left IFC | NS | 61.1 (8.0) | 48 (44) | no | no | 6 | Both | SSF, word span, DSF, digit span with a pointing response, 2-back task | -1.72 .19 |
| Beeson et al., 1993* | 7 anterior LH, 7 posterior LH | NS | 65.3 (7.0) | 44 (NS) | no | no | 14 | low | DSF, SSF | -1.39 .14 |
| Bugarski Ignjatovic et al., 2015 | 40 | IS | Median NS [45-78] | < 1 | no | no | 40 | low | DSF, SSF | NA |
| Burton et al., 2004 | 69 | NS | 80.2 (4.1) | 3 (NS) | NS | no | 23 | low | memory scanning (CDR) | NA |
| Butler et al., 2009* | 9 neglect, 11 RH | NS | 61.1 (14.9) | 2.6 (1.7) | NS | NS | 10 | both | DSF, DSB | -.65 .10 |

**Table S1** Continued

| Study | Patients N subgroups/ specific incl. | Stroke type | Age M (SD) or Median [range] | Interval¹ in months M (SD) [range] | Prior stroke | Prior dementia | Healthy controls | Low-/ high- load | Task | Hedges's g, Variance |
|---|---|---|---|---|---|---|---|---|---|---|
| Cao et al., 2007* | 40 | IS | 38.8 (8.3) | 9.2 [6-12] | no | NS | 40 | both | DSF, DSB, SSF | -.40 / .05 |
| Danet et al., 2015 | 12 left thalamic | IS | 53.2 (14.6) | 19 [3-59] | no | no | 25 | both | DSF, SDB, SSF, SSB | NA |
| Elwan et al., 1994* | 23 acute, 34 chronic | IS and TIA | 59.1 (7.9) | acute < 1; chronic 12 (12) | NS | no | 30 | high | PASAT | -.54 / .02 |
| Exner et al., 2001* | 15 thalamic, 22 basal ganglia | IS and HS | 54.8 (10.5) | 36 (34) | no | no | 15 | both | DSF, DSB | -.28 / .06 |
| Fu et al., 2017 | 34 brainstem | NS | 59.6 (12.7) | < 1 | no | no | 26 | both | DST | NA |
| Godefroy et al., 1994 | 11 lenticulostriate | NS | 56.5 (NS) | [1.5 – 2] | no | no | 11 | low | DSF, SSF | NA |
| Gong et al., 2015* | 25 occipital | NS | 60.9 (11.0) | [.5 – 2] | NS | no | 29 | both | DSF, DSB | -.40 / .07 |
| Gorišek et al., 2016 | 10 left MCA | IS | 67 (NS) | 1.8 (1) | no | no | 10 | low | Sternberg task | NA |
| Grosdemange et al., 2015* | 28 | IS | 67.5 (8.3) | < 1 | no | no | 41 | both | DSF, DSB, SSF, SSB | .14 / .06 |
| Hirel et al., 2017 | 10 LH, 10 RH | IS | 60.6 (11.7) | 17 (15) | no | no | 14 | low | experimental word, tone, visual STM tasks | NA |
| Ho et al., 2018 | 15 LH, 10 RH | NS | 56.3 (8.9) | 92 (78) | no | no | 25 | low | ISR 7 variants | NA |
| Hochstenbach et al., 1998a* | 199 | IS and HS | 55.9 (11.2) | 2.4 (1.6) | yes | NS | 32 | both | DSF, DSB | -.72 / .04 |
| Hochstenbach et al., 1998b | 12 basal ganglia | IS and HS | 53.4 (NS) | < 3 | NS | NS | 24 | both | DSF, DSB | NA |
| Jokinen et al., 2006* | 321 | IS | 70.3 (7.6) | 3 (NS) | yes | yes | 38 | both | DSF, DSB | -.43 / .03 |
| Kant et al., 2014* | 39 | IS and HS | 58.2 (14.2) | 17 (8.3) | NS | no | 53 | both | Letter Number Sequencing, SSF, SS | -.69 / .05 |
| Karimian et al., 2018 | 35 | IS | 61.7 (NS) | < 12 | no | no | 35 | both | DSF, SDB, SSF, SSB | NA |
| Kessels et al., 2002* | 28 LH, 16 RH, 6 BL | IS | 52.4 (13.0) | 26 (22) | no | no | 39 | low | SSF | -.66 / .05 |
| Kober et al., 2015 | 24 | NS | Median NS [37-82] | > 1 | no | no | 40 | both | DSF, DSB, SSF, SSB | NA |
| Kokubo et al., 2015* | 15 putaminal | HS | 53.0 (10.2) | 2 (.2) | no | no | 15 | high | Letter Number Sequencing | -1.84 / .18 |
| Kraft et al., 2015* | 16 thalamic | NS | 41.2 (11.0) | 36 (42) | no | no | 52 | low | Experimental task based on TVA | -.59 / .08 |
| Leskelä et al., 1999 | 62 frontal, 188 non-frontal | IS | 70.5 (7.6) | 3.4 (.4) | yes | yes | 39 | both | DSF, DSB | NA |
| Li et al., 2013* | 21 | TIA | 50.1 (6.5) | < 1 | no | no | 21 | high | DSB | -.21 / .09 |
| Li et al., 2019 | 68 | minor stroke | 60.3 (12.1) | < .5 | no | no | 36 | both | DSF, DSB | NA |
| Liebermann et al., 2013* | 19 thalamic | IS | 44.6 (11.1) | 29 (35) | NS | NS | 20 | both | DFS, DSB, SSF, SSB | -.42 / .10 |
| Low et al., 2016* | 12 LH, 15 RH, 3 RH neglect, 10 TIA | IS and TIA | 58.3 (9.4) | 7.0 (3.9) IS; 3.9 (1.9) TIA; T2 + 3 | no | no | 31 | both | visual variant of DSF and DSB | -.55 / .04 |
| Luukkainen-Markkula et al., 2011 | 11 RH neglect | NS | 58.7 (9.8) | 2.5 (2.1) | no | NS | 12 | low | SSF | -2.23 / .27 |
| Malhotra et al., 2005 | 10 RH, 10 RH neglect | NS | 66.0 (13.9) | 67 (58) | NS | NS | 10 old 10 young | low | computerized spatial span task | NA |
| Malm et al., 1998 | 24 cerebellum or brainstem | IS | 36.9 (6.5) | .5 (NS) | NS | NS | 14 | low | DSF, DSB, sentence span task, word span | NA |

**Table S1** Continued

| Study | Patients N subgroups/ specific incl. | Stroke type | Age M (SD) or Median [range] | Interval¹ in months M (SD) [range] | Prior stroke | Prior dementia | Healthy controls | Low-/high-load | Task | Hedge's g, Variance |
|---|---|---|---|---|---|---|---|---|---|---|
| Malouin et al., 2004 | 12 supratentorial | NS | 56.1 (9.9) | 18 (14) | no | NS | 14 | low | forward visuospatial, verbal, and kinesthetic span tasks | NA |
| Mansueti et al., 2008* | 24 study 1, 24 study 2 | minor stroke | 71.0 (9.2) | Self-report | no | no | Study 1 24 Study 2 24 | high | reading span, computational span | -.23 .04 |
| Martin et al., 2019* | 32 LH | IS | 63.5 (12.7) | < .25 | no | no | 13 | low | digit match span, category probe span | -1.40 .13 |
| Martins et al., 2009* | 22 LH | NS | Median NS [31-80] | >3 | no | NS | 22 | both | DSF, DSB | -2.03 .14 |
| McDonnel et al., 2011 | 17 | IS and HS | 70.1 (NS) | 107 (NS) | NS | no | 13 | both | DSF, DSB, SSF, SSB, PASAT | NA |
| Nys et al., 2007* | 168 | IS and HS | 62.7 (13.8) | < .75 | no | no | 77 | both | DST, SSF | -.68 .02 |
| Oliveira et al., 2015* | 42 RH | IS and HS | 58.3 (11.8) | 20 (24) | no | no | 84 | high | ADO, AS | -.47 .03 |
| Pergola et al., 2012* | 9 paramedian, 8 tuberothalamic | IS | 62 (12) | 67 (48) | no | no | 28 | both | DSF, SDB, SSF, SSB | -1.85 .14 |
| Piccardi et al., 2016* | 346 | NS | 63.7 (14.3) | 2.2 (7.2) | no | no | 272 | both | DSF, SDB, SSF, SSB | .07 .01 |
| Planton et al., 2012 | 60 | IS | 59.7 (14) | 3.6 (.7) | no | no | 40 | both | DSF, SDB, SSF, SSB | NA |
| Pluta et al., 2017 | 29 RH, 24 LH, 5 BL | NS | 57.7 (12.9) | 25 (31) | no | no | 33 | both | DST | NA |
| Ramsey et al., 2017* | T1 108, T2 91, T3 88 | IS and HS | 54 (10) | .5, 3, 12 | no | no | 31 | both | SSF, SSB | -.42 .02 |
| Rapport et al., 1994* | 29 RH neglect, 22 RH no neglect | NS | 62.2 (6.7) | 5.8 (10.1) | NS | NS | 20 | both | DSF, DSB | -.35 .05 |
| Ravizza et al., 2005* | 10 cerebellar | IS | 61.3 (16.6) | chronic, NS | NS | NS | 15 | both | DSF, DSB, SSF, SSB | -.47 .17 |
| Rochat et al., 2013* | 55 | IS and HS | 56.4 (13.1) | 24.1 (36.1) | no | no | 15 | high | Letter-Number Sequencing | -.79 .09 |
| Rosemann et al., 2017* | 20 MCA | NS | 52 (9.8) | < .25 | no | no | 20 | high | 2-back | -.49 .10 |
| Rousseaux et al., 2008* | 20 AChAI | NS | 59.6 (12.39) | 1.5 (.6) | no | no | 20 | both | DSF, SDB, SSF | .17 .10 |
| Roussel et al., 2012* | 17 frontal, 12 posterior | IS and HS | 45.5 (12.9) | <1 | no | no | 29 | both | DSF, DSB, experimental consonant span, word span, spatial span SS (visual and auditory) | -.61 .05 |
| Sachdev et al., 2006* | 139 | IS and TIA | 72.2 (9.0) | [3-6] | no | no | 100 | both | DSF, DSB | -.41 .01 |
| Sachdev et al., 2009 | 104 | IS and TIA | 70.4 (9.2) | [3-6], follow-up + 36 | no | no | 84 | both | DSF, DSB | NA |
| Saldert et al., 2007* | 14 RH, 14 LH | NS | 62.6 (NS) | > 6 | NS | NS | 14 | low | experimental Reading Span test | -1.01 .08 |
| Salis et al., 2018* | 12 aphasia | IS and HS | 54.8 (9.6) | 61 (53) | NS | NS | 7 | low | Word span | -4.10 .65 |
| Schaapsmeerders et al., 2013* | 277 | IS | 50.9 (10.3) | 132 (98) | no | NS | 146 | low | PPMST | -.85 .01 |
| Schoo et al., 2014* | 40 | IS | 64 (10.7) | < .5 | no | no | 31 | both | DSF, DSB | .50 .06 |
| Schweinberger et al., 1992* | 16 LH, 14 RH | IS and HS | 50.2 (11.2) | 19 (NS) | NS | NS | 14 | both | DSF, SDB, SSF, SSB | -.47 .07 |
| Selnes et al., 2015 | 27 | IS | 63.7 (NS) | 3 (NS) | NS | no | 41 | high | Letter-number sequencing | NA |
| Snaphaan et al., 2009* | 28 | IS | 53.7 (12.6) | [1.5 – 3] | no | no | 22 | high | 2-back | -.40 .08 |

**Table S1** Continued

| Study | Patients N subgroups/ specific incl. | Stroke type | Age M (SD) or Median [range] | Interval¹ in months M (SD) [range] | Prior stroke | Prior dementia | Healthy controls | Low-/high-load | Task | Hedges's g, Variance |
|---|---|---|---|---|---|---|---|---|---|---|
| Srikanth et al., 2003 | 99 | IS and HS | 70.5 (14.0) | 3 (NS) | no | yes | 99 | both | DST | NA |
| Stamenova et al., 2017* | 17 | NS | 67.1 (10.8) | 53 (NS) | NS | no | 30 | both | DSF, DSB | .20 .09 |
| Stricker et al., 2010 | 42 | NS | 63.2 (10.6) | 96 (75.6) | NS | NS | 36 | both | DSF, DSB | NA |
| Su et al., 2018* | 25 RH | TIA | 52.4 (4.9) | .25, T2 3 | no | no | 25 | high | 2-back | -.57 .04 |
| Van Asselen et al., 2009* | 21 RH, 32 LH, 5 BL | IS and HS | 54.5 (2.9) | > 6 | NS | no | 76 | low | SSF | -.42 .06 |
| Van Asselen et al., 2006* | 14 RH, 16 LH | NS | 57.8 (2.9) | > 6 | NS | no | 36 | both | Letter number sequencing, SSF | -2.34 .03 |
| Van der Ham et al., 2012 | 16 LH, 17 RH | IS and HS | 59.2 (13.3) | 14 (5) | no | no | 28 | both | Letter number sequencing, SSF, SSB | NA |
| Van Geldorp et al., 2013* | 24 | IS and HS | 52.1 (11.2) | chronic | NS | NS | 31 | both | DST | -.54 .10 |
| Van Zandvoort et al., 2001* | 35 SSLI | IS | 59 (13) | <.5, T2 7 (2) | no | no | 31 | both | DST, SSF | -.62 .03 |
| Volle et al., 2008* | 20 | IS and HS | 45.6 (11.3) | 18.3 (16.8) | no | NS | 48 | both | 1-, 2-, 3-back | -.83 .08 |
| Weinstein et al., 2014* | 132 | IS and HS | 77.4 (9.4) | 6 (NS) | NS | no | 132 | both | DSF, DSB | -.41 .02 |

*Notes*. articles with an asterisk (*) are included in the meta-analyses, other articles are only included in the systematic review. ¹Interval between stroke and working memory assessment. IS = ischemic stroke; HS = haemorrhagic stroke; LH = left hemisphere; RH = right hemisphere; BL = bilateral; IPC = inferior parietal cortex; IFC = inferior frontal cortex; MCA = middle cerebral artery; AChAI = anterior choroidal artery infarction; SSLI = single supratentorial lacunar infarct; WB = whole brain; NS = not specified; NA = not applicable; DSF = digit span forward; DSB = digit span backward; DST = digit span total; SSF = spatial span forward; SSB = spatial span backward; CDR = Cognitive Drug Research; ADO = ascendant ordering of digits; AS = auditory span of words in sentences; PPMST = Paper and Pencil Memory Scanning Task; ISR = Immediate Serial Recall; PASAT = Paced Auditory Serial Addition Test; TVA = theory of visual attention.

**Table S2** RTI items rated for all studies

| | Q1 | Q2 | Q3 | Q5 | Q6 | Q7 | Q8 | Q9 | Q13 |
|---|---|---|---|---|---|---|---|---|---|
| Andrade et al., 2012 | low | low | low | Low | Low | low | N/A | high | high |
| Andrews et al., 2013 | uncl | low | low | uncl | low | high | N/A | low | high |
| Andrews et al., 2014 | uncl | low | low | uncl | low | high | N/A | low | high |
| Baier et al., 2014 | uncl | uncl | uncl | uncl | low | low | N/A | high | high |
| Baldo et al., 2006 | low | P low; HC uncl | low | uncl | low | low | N/A | low | low |
| Beeson et al., 1993 | P low; HC uncl | uncl | low | uncl | low | high | N/A | low | high |
| Bugarski Ignjatovic et al., 2015 | low | P low; HC uncl | low | uncl | low | low | N/A | high | low |
| Burton et al., 2004 | low | low | high | uncl | low | low | N/A | low | high |
| Butler et al., 2009 | uncl | uncl | high | uncl | low | low | N/A | low | high |
| Cao et al., 2007 | P low; HC uncl | P low; HC uncl | low | uncl | low | low | N/A | low | high |
| Danet et al., 2015 | P low; HC uncl | P low; HC uncl | low | uncl | low | low | N/A | low | high |
| Elwan et al., 1994 | low | low | high | uncl | low | high | N/A | low | high |
| Exner et al., 2001 | low | low | low | uncl | low | high | N/A | low | low |
| Fu et al., 2017 | P low; HC uncl | P low; HC uncl | low | uncl | low | low | N/A | high | uncl |
| Godefroy et al., 1994 | P low; HC uncl | low | low | uncl | low | low | N/A | high | uncl |
| Gong et al., 2015 | low | low | low | uncl | uncl | low | N/A | high | high |
| Gorišek et al., 2016 | P low; HC uncl | uncl | uncl | uncl | low | low | N/A | low | high |
| Grosdemange et al., 2015 | low | low | low | high | low | low | N/A | low | low |
| Hirel et al., 2017 | low | P low; HC uncl | low | uncl | low | low | N/A | high | low |
| Ho et al., 2018 | P low; HC uncl | uncl | low | uncl | low | low | N/A | high | high |
| Hochstenbach et al., 1998a | low | low | low | uncl | low | high | N/A | low | low |
| Hochstenbach et al., 1998b | low | low | low | uncl | low | high | N/A | high | low |

**Table S2** Continued

| | Q1 | Q2 | Q3 | Q5 | Q6 | Q7 | Q8 | Q9 | Q13 |
|---|---|---|---|---|---|---|---|---|---|
| Jokinen et al., 2006 | low | low | high | uncl | low | uncl | N/A | high | high |
| Kant et al., 2014 | low | low | low | uncl | low | low | N/A | low | high |
| Karimian et al., 2018 | low | P low; HC uncl | high | high | low | high | N/A | high | low |
| Kessels et al., 2002 | P low; HC uncl | low | low | uncl | low | low | N/A | high | high |
| Kober et al., 2015 | P low; HC uncl | uncl | high | uncl | uncl | high | N/A | high | high |
| Kokubo et al., 2015 | P low; HC uncl | low | low | low | low | low | N/A | low | high |
| Kraft et al., 2015 | low | P low; HC uncl | high | uncl | low | high | N/A | high | high |
| Leskelä et al., 1999 | P low; HC uncl | low | high | low | low | low | N/A | low | high |
| Li et al., 2013 | low | uncl | low | uncl | low | low | N/A | high | high |
| Li et al., 2019 | low | low | low | uncl | low | low | N/A | low | high |
| Liebermann et al., 2013 | low | low | low | uncl | low | high | N/A | high | high |
| Low et al., 2016 | low | low | high | uncl | low | high | N/A | low | high |
| Luukkainen-Markkula et al., 2011 | uncl | P low; HC uncl | low | uncl | low | high | N/A | low | high |
| Malhotra et al., 2005 | uncl | low | high | uncl | low | high | N/A | high | high |
| Malm et al., 1998 | uncl | P low; HC uncl | high | uncl | low | uncl | low | high | high |
| Malouin et al., 2004 | P low; HC uncl | uncl | high | uncl | uncl | low | N/A | high | high |
| Mansueti et al., 2008 | low | low | low | uncl | high | uncl | N/A | low | low |
| Martin et al., 2019 | P low; HC uncl | P low; HC uncl | uncl | uncl | low | low | N/A | low | high |
| Martins et al., 2009 | low | low | low | uncl | low | uncl | N/A | high | high |
| McDonnell et al., 2011 | low | low | low | high | low | low | N/A | high | high |
| Nys et al., 2006 | low | P low; HC uncl | high | uncl | uncl | low | N/A | low | low |
| Oliveira et al., 2015 | low | uncl | low | uncl | uncl | uncl | N/A | high | low |
| Pergola et al., 2012 | low | P low; HC uncl | low | uncl | low | low | N/A | low | low |
| Piccardi et al., 2016 | low | P low; HC uncl | low | uncl | uncl | high | N/A | high | uncl |
| Planton et al., 2012 | low | low | low | uncl | low | low | N/A | high | low |
| Pluta et al., 2017 | P low; HC uncl | uncl | low | uncl | uncl | high | N/A | high | low |
| Ramsey et al., 2017 | low | P low; HC uncl | low | uncl | low | low | low | high | low |
| Rapport et al., 1994 | uncl | uncl | low | uncl | uncl | high | N/A | low | high |
| Ravizza et al., 2005 | uncl | uncl | low | uncl | low | uncl | N/A | high | high |
| Rochat et al., 2013 | P low; HC uncl | low | low | uncl | low | low | low | low | high |
| Rosemann et al., 2017 | low | P low; HC uncl | high | uncl | uncl | low | N/A | low | high |
| Rousseaux et al., 2008 | P low; HC uncl | low | low | uncl | low | low | N/A | high | high |
| Roussel et al., 2012 | P low; HC uncl | P low; HC uncl | low | uncl | low | low | N/A | low | high |
| Sachdev et al., 2006 | low | low | high | uncl | low | low | low | high | low |
| Sachdev et al., 2009 | low | low | high | uncl | low | low | low | high | low |
| Saldert et al., 2007 | low | P low; HC uncl | low | uncl | low | low | N/A | high | high |
| Salis et al., 2018 | uncl | uncl | high | uncl | uncl | low | N/A | low | high |
| Schaapsmeerders et al., 2013 | low | low | low | uncl | low | low | low | low | low |
| Schoo et al., 2014 | low | P low; HC uncl | low | uncl | low | low | N/A | high | low |
| Schweinberger et al., 1992 | P low; HC uncl | P low; HC uncl | low | uncl | low | high | N/A | low | high |
| Selnes et al., 2015 | P low; HC uncl | low | high | uncl | uncl | uncl | N/A | high | high |
| Snaphaan et al., 2009 | P low; HC uncl | P low; HC uncl | low | uncl | low | low | N/A | low | high |
| Srikanth et al., 2003 | P low; HC uncl | low | low | low | low | uncl | N/A | high | high |
| Stamenova et al., 2017 | low | low | low | uncl | uncl | low | N/A | low | high |
| Stricker et al., 2010 | low | P low; HC uncl | low | uncl | low | low | N/A | high | high |
| Su et al., 2018 | low | unclear | low | uncl | low | low | low | low | low |
| Van Asselen et al., 2009 | low | low | low | uncl | low | low | N/A | low | low |
| Van Asselen et al., 2006 | P low; HC uncl | low | low | uncl | uncl | low | N/A | low | high |
| Van der Ham et al., 2012 | P low; HC uncl | P low; HC uncl | low | uncl | low | low | N/A | low | high |
| Van Geldorp et al., 2013 | uncl | P low; HC uncl | low | uncl | uncl | uncl | N/A | high | high |
| Van Zandvoort et al., 2001 | P low; HC uncl | P low; HC uncl | low | uncl | low | low | N/A | low | high |
| Volle et al., 2008 | low | P low; HC uncl | low | uncl | low | high | N/A | low | high |
| Weinstein et al., 2014 | low | low | low | uncl | low | low | N/A | low | high |

*Notes.* P = patient; HC = healthy control; uncl = unclear or not reported; N/A = not applicable

**Table S3a** Results of the meta-analyses after exclusion of studies that included TIA patients.

|  | k | N P/HC | ES (g) | 95% CI | Q | p (Q) | I² | τ² | Fail-safe N |
|---|---|---|---|---|---|---|---|---|---|
| Overall | 46 | 2,750/2,506 | -.68 | -.85 to -.52 | 285.35 | <.001 | 84.23 | .25 | 4,202 |
| Low-load | 38 | 2,550/2,087 | -.59 | -.79 to -.40 | 308.01 | <.001 | 87.99 | .31 | 2,234 |
| High - load | 37 | 2,141/1,916 | -.62 | -.78 to -.46 | 171.10 | <.001 | 78.96 | .18 | 2,231 |
| Sub - actute | 12 | 759/395 | -.44 | -.72 to -.16 | 44.78 | <.001 | 75.44 | .18 | 104 |
| Chronic | 21 | 1,026/1,117 | -.93 | -1.20 to -.67 | 146.33 | <.001 | 86.33 | .31 | 1,587 |

*Notes. k* = number of studies; P = patients; HC = healthy controls

**Table S3b** Results of the meta-analyses based on span tasks only.

|  | k | N P/HC | ES (g) | 95% CI | Q | p (Q) | I² | τ² | Fail-safe N |
|---|---|---|---|---|---|---|---|---|---|
| Overall | 31 | 2,155/1,805 | -.61 | -.81 to -.40 | 231.68 | <.001 | 87.05 | .28 | 1,578 |
| Low- load | 30 | 2,201/1,787 | -.55 | -.76 to -.34 | 235.23 | <.001 | 87.67 | .28 | 1,278 |
| High- load | 26 | 1,883/1,433 | -.52 | -.71 to -.34 | 130,00 | <.001 | 80.77 | .17 | 855 |
| Sub-acute | 8 | 656/288 | -.19 | -.48 to .10 | 23.34 | .001 | 70.01 | .12 | 9 |
| Chronic | 13 | 622/880 | -.87 | -1.26 to -49 | 129.99 | <.001 | 90.77 | .44 | 570 |

*Notes. k* = number of studies; P = patients; HC = healthy controls

## Nederlandse samenvatting

Onze omgeving bestaat uit voorwerpen en taferelen die vele visuele eigenschappen hebben: vorm, kleur, textuur, locatie, grootte en oriëntatie. Mensen zijn in staat om een interne representatie van deze eigenschappen te vormen en van combinaties van eigenschappen die samen een object vormen. Sommige van deze representaties onthouden we over een korte periode, andere onthouden we over langere tijd. Het vermogen om beelden die we gezien hebben te onthouden is essentieel voor veel van onze dagelijkse activiteiten.

Om beter te begrijpen hoe ons geheugen werkt, is het van belang te onderzoeken hoe verschillende geheugenprocessen zich tot elkaar verhouden. De vraag is bijvoorbeeld of er verschillende systemen verantwoordelijk zijn voor het vasthouden van informatie over verschillende tijdsintervallen. Hierbij kan onderscheid gemaakt worden tussen het werkgeheugen (vasthouden of manipuleren van informatie gedurende een korte periode waarin de aandacht wordt vastgehouden) en langetermijngeheugen (het opdiepen en opnieuw activeren van informatie op een later tijdstip). Er zijn verschillende vormen van het langetermijngeheugen, dit proefschrift richt zich alleen op het episodisch geheugen; het geheugen voor persoonlijke gebeurtenissen. Veel geheugenonderzoek is gedaan met verbale taken, terwijl de interactie met de wereld om ons heen een sterke visuele component heeft.

Dit proefschrift beschrijft studies waarin naar verschillende subsystemen van geheugen is gekeken aan de hand van visuele geheugentaken. Om inzicht te krijgen in onderliggende mechanismen is onderzoek gedaan naar hoe veroudering verschillende geheugensystemen beïnvloed en wat de gevolgen zijn van hersenenschade op deze geheugenprocessen.

**Hoofdstuk 2** betreft een studie naar het werkgeheugen en episodisch geheugen, gemeten aan de hand van een nieuw ontwikkelde taak, met als vraagstelling of deze twee geheugenfuncties op eenzelfde manier worden beïnvloed door leeftijd. In deze taak vormt één enkele aanleerfase (waarin afbeeldingen van alledaagse voorwerpen op verschillende posities van het computerscherm getoond werden) de basis voor zowel de werkgeheugentest als de episodische geheugentest. De resultaten lieten zien dat ouderen (62+) op deze taak slechter presteerden dan jongvolwassenen (20-29 jaar), maar dat dit in dezelfde mate gold voor het werkgeheugen als het episodisch geheugen. Een interessante bevinding is dat bij jongvolwassenen de prestatie op de werkgeheugentest en de episodische geheugentest samenhing, terwijl dit niet het geval was bij ouderen. De relatie tussen werkgeheugen en episodisch geheugen is dus leeftijdsafhankelijk. Dit is een indicatie dat verschillende cognitieve processen een rol spelen bij deze twee geheugenprocessen.

In **hoofdstuk 3** is dezelfde taak gebruikt om geheugenfuncties van patiënten met hersenschade ten gevolge van een herseninfarct te vergelijken met ouderen zonder infarct. Het doel van deze studie was om twee theorieën met elkaar te vergelijken. De ene theorie gaat uit van gescheiden geheugenopslag voor werk-geheugen en langetermijngeheugen terwijl de andere theorie het werkgeheugen beschouwt als een actief onderdeel van het langetermijngeheugen. Er is gekeken naar de prestatie op beide testonderdelen en naar de relatie tussen de geheugen-prestaties en de plaats van de hersenbeschadiging. Het vermogen om eerder geleerde informatie (voorwerpen) te herkennen in de juiste context (locatie of volgorde) bleek gebaseerd te zijn op verschillende systemen voor het werk-geheugen en episodisch geheugen. Analyses van de hersenschade zelf (de laesies) gaven aanwijzingen dat verschillende onderdelen van de fasciculus arcuatus (een wittestofbaan die hersengebieden met elkaar verbindt) sterker met het werk-geheugen, dan wel met het episodisch geheugen, samenhingen. De antwoord-tendentie bleek vergelijkbaar voor de werkgeheugentest en de episodische geheugentest. Deze resultaten waren gedeeltelijk in lijn met de theorie van gescheiden geheugensystemen.

Theorieën die uitgaan van gescheiden geheugensystemen stellen dat er meerdere representaties van dezelfde informatie in de hersenen zijn. **Hoofdstuk 4** betreft een studie naar representaties in het werkgeheugen. De vraagstelling in hoofdstuk 4 is of een herseninfarct effect kan hebben op het vormen van een geïntegreerde representatie van meerdere visuele kenmerken. Het vormen van geïntegreerde representaties is cruciaal voor het succesvol onthouden van gebeurtenissen – die we immers niet als losse onderdelen onthouden, maar als één geheel. In deze studie is gebruik gemaakt van een taak waarbij deelnemers kort een aantal gekleurde cirkels te zien kregen op een computerscherm en vervolgens op basis van één van de eigenschappen – kleur of locatie – van één van de items, de andere eigenschap van dat item moesten aangeven. Patiënten die een herseninfarct gehad hebben waren minder precies in het aanduiden van zowel de kleur als de locatie, maar maakten niet meer fouten door het aangeven van eigenschappen die bij andere items hoorden (integreren). De nauwkeurigheid in het rapporteren van eigenschappen en het vermogen deze eigenschappen te integreren hingen samen met verschillende laesieprofielen. De resultaten suggereren dat representaties in verschillende locaties in de hersenen worden opgeslagen. Hierdoor kan mogelijk compensatie optreden voor beschadigde hersengebieden waardoor patiënten met een herseninfarct slechts subtiele afwijkingen hebben in het visueel werkgeheugen.

Hoofdstuk 4 liet zien dat patiënten met een herseninfarct slechts subtiele problemen hebben in het visueel werkgeheugen. De meta-analyse beschreven in **hoofdstuk 5** concludeert echter dat een herseninfarct wel degelijk tot werkge-

heugenproblemen kan leiden. Werkgeheugenproblemen na een herseninfarct bleken voor te komen in alle componenten van werkgeheugen; het effect was vergelijkbaar voor taken met een lage werkgeheugenbelasting (alleen onthouden en reproduceren), een hoge belasting (manipuleren van informatie), en voor verbaal en non-verbaal studiemateriaal. Een andere belangrijke bevinding was dat werkgeheugenproblemen ook in de chronische fase na een herseninfarct nog prominent aanwezig waren.

Niet alleen werkgeheugenproblemen komen veelvuldig voor na een hersen-infarct, ook episodische geheugenproblemen komen regelmatig voor. In **hoofdstuk 6** is gekeken naar het voorkomen van verschillende profielen van vergeten bij patiënten met een herseninfarct. Het visueel episodisch geheugen is gemeten op drie verschillende momenten: directe herkenning (T1), herkenning na een kort interval (20 minuten, T2), en herkenning na een lang interval (één week later, T3). Patiënten werden ingedeeld in drie verschillende groepen op basis van hun vergeetscore in vergelijking met een controlegroep: patiënten zonder geheugen-problemen ($N$ = 64), patiënten die snel vergeten ($N$ = 12), en patiënten die alleen meer vergeten na een lang interval ($N$ = 15). Alle patiënten bleken minder zeker waren over hun geheugenprestaties in vergelijking met controles, onafhankelijk van hun werkelijke prestatie. Deze studie liet verder zien dat er een groep patiënten is die nog goed presteert na een kort interval, maar die problemen laat zien met het onthouden van informatie gedurende een langer interval. Standaard wordt in de klinische praktijk echter alleen getest op geheugenproblemen na een relatief kort interval van 20-30 minuten. Mogelijk wordt hierdoor een groep patiënten met geheugenproblemen niet geïdentificeerd.

Samenvattend toont het onderzoek in dit proefschrift aan dat er verschillende vormen zijn van visuele geheugenproblemen bij ouderen en bij patiënten die een herseninfarct hebben gehad. Tevens laat het zien dat visuele representaties verspreid zijn over de hele hersenen.

## Dankwoord

Na vijf jaar onderzoek doen is het klaar. Of misschien niet echt klaar, er moeten nog artikelen herschreven worden en er zijn nog meer dan genoeg ideeën voor vervolgartikelen, maar op het moment dat ik dit schrijf is mijn proefschrift goed-gekeurd dus dat deel is in elk geval klaar. Ik heb met veel plezier aan dit proefschrift gewerkt, ook als dat soms lange dagen (en nachten) waren en ook als hele delen van het werk opnieuw gedaan moesten worden. Ik ben dankbaar voor de steun die ik op veel verschillende manieren heb mogen ontvangen tijdens dit leerzame proces.

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Frank Erik, jij was voor mij de connectie met de kliniek, zowel in de praktijk als in de manier van denken. Bij presentaties en artikelen stelde je steevast de vraag "Wat betekent dit nu voor mij als neuroloog of voor de patiënt?". Een vraag die ik vaak moeilijk vond om te beantwoorden maar die me wel elke keer kritisch liet nadenken over het onderzoek dat ik deed. Naast een kritische vragensteller ben je ook een zeer goede gastheer zoals elk jaar duidelijk werd bij het zomerse etentje voor PhD's bij jou in de tuin.

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Fijne, gezellige, lieve collega's van het DCC, bedankt! Nikki en Johanna, jullie zijn de beste kamergenoten. Saskia, fijn dat je altijd alles weet en dat ik ook voor een luisterend oor binnen kon lopen. Vitória, bedankt voor alle moeite die je gedaan hebt voor mij met betrekking tot het cluster en je betrokkenheid. Ileana, onze onderzoeken liepen parallel en regelmatig konden we gefrustreerd of juist blij bij elkaar binnen lopen als er iets was met analyses, succes verder! In het kader van DCC-borrels, zeilweekenden, tramparty, dansen en feestjes, Sanne, Sybrine, Willeke, Max, Fenny, Xiaochen, Josi, Syanah, Sebo, bedankt!

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## Curriculum Vitae

Selma Lugtmeijer is op 5 mei 1989 geboren in Zaanstad. Na afronding van het tweetalig vwo aan het Overbetuwe College in Bemmel in 2007 is zij gestart met de studie Orthopedagogische Wetenschappen en Onderwijskunde aan de Radboud Universiteit in Nijmegen die zij in 2010 heeft afgerond. In 2011 is ze begonnen met een masteropleiding Pedagogische wetenschappen aan de Vrije Universiteit in Amsterdam. De wetenschappelijke stage betrof een onderzoek naar zelfconcept van jongvolwassenen met verschillende etnische achtergronden. Van 2012 tot 2014 volgde Selma de onderzoeksmaster Cognitive Neuropsychology aan de Vrije Universiteit. In het kader van haar scriptie deed ze onderzoek bij het Donders Instituut naar werkgeheugen bij volwassenen met ADHD aan de hand van experimentele taken, neuroimaging en genetica. Aansluitend is ze gaan werken als onderzoeksassistent binnen ditzelfde project. Selma begon haar promotie-onderzoek in mei 2015. Dit betrof een gecombineerde aanstelling aan de Universiteit van Amsterdam, het Donders Instituut van de Radboud Universiteit en het Radboudumc. Dit project bood de ideale combinatie van patiëntencontact en onderzoek doen naar fundamentele vragen over hoe geheugen in het brein werkt. Ook bood het de mogelijkheid om met verschillende technieken onderzoek te doen, zoals neuropsychologisch onderzoek, experimentele taken, eyetracking en neuroimaging. Ze onderzocht de relatie tussen verschillende geheugensystemen bij veroudering en patiënten met hersenschade ten gevolge van een infarct. De belangrijkste resultaten zijn in dit proefschrift beschreven. Selma kijkt er naar uit om haar loopbaan voort te zetten in de wetenschap.

## Author contributions

**Chapter 2**

Lugtmeijer, S., de Haan, E. H. F., & Kessels, R. P. C. (2019). A comparison of visual working memory and episodic memory performance in younger and older adults. *Aging, Neuropsychology, and Cognition*, *26*(3), 387-406.

Conceptualization: SL, RPCK; methodology: SL, RPCK; data collection: SL; analysis: SL; writing (original draft): SL; writing (review and editing): EHFdH, RPCK.

**Chapter 3**

Lugtmeijer, S., Geerligs, L., De Leeuw, H. F., De Haan, E. H. F., Kessels, R. P. C., on behalf of The Visual Brain Group. Are visual working memory and episodic memory distinct processes? Insight from stroke patients by lesion-symptom mapping. – *Submitted*

Conceptualization: SL, RPCK; methodology: SL, LG; data collection: SL, Visual Brain Group; analysis: SL, LG; writing (original draft): SL; writing (review and editing): LG, HFdL, EHFdH. RPCK.

**Chapter 4**

Lugtmeijer, S.*, Schneegans, S.*, Lammers, N. A., Geerligs, L., De Leeuw, F. E., De Haan, E. H. F., Bays, P. M., & Kessels, R. P. C.. Consequence of stroke for feature recall and binding in visual working memory. * shared authorship – *Submitted*

Conceptualization: SL, SS, PMB, RPCK; methodology: SL, SS, LG, PMB; data collection: SL, NAL; analysis: SL, SS; writing (original draft): SL, SS; writing (review and editing): LG, HFdL, EHFdH, PMB, RPCK.

**Chapter 5**

Lugtmeijer, S., Lammers, N. A., De Haan, E. H. F., De Leeuw, H. F., Kessels, R. P. C. (2019). Post-stroke working memory dysfunction: A meta-analysis and systematic review. *Neuropsychology reviews – In press*

Conceptualization: SL, RPCK; methodology: SL; data collection: SL, NAL; analysis: SL; writing (original draft): SL; writing (review and editing): NAL, EHFdH, HFdL, RPCK.

**Chapter 6**

Lammers, N. A., Lugtmeijer, S., De Haan, E. H. F., & Kessels, R. P. C.. Accelerated long term forgetting: The influence of a prolonged delay on sensitivity of memory assessment and metacognitive confidence in stroke patients and healthy controls. — *Submitted*

Conceptualization: NAL; methodology: NAL, SL; data collection: NAL, SL; analysis: NAL, SL; writing (original draft): NAL; writing (review and editing): SL, EHFdH, RPCK.

## Publications

**Lugtmeijer, S.**, de Haan, E. H. F., & Kessels, R. P. C. (2019). A comparison of visual working memory and episodic memory performance in younger and older adults. *Aging, Neuropsychology, and Cognition*, *26*(3), 387-406.

Bruijnen, C. J., Jansen, M., Dijkstra, B. A., Walvoort, S. J., **Lugtmeijer, S.**, Markus, W., ... & Kessels, R. P. (2019). The Montreal Cognitive Assessment (MoCA) as a cognitive screen in addiction health care: A validation study for clinical practice. *Journal of Substance Use*, *24*(1), 47-54.

**Lugtmeijer, S.**, Lammers, N. A., De Haan, E. H. F., De Leeuw, H. F., Kessels, R. P. C. (2019). Post-stroke working memory dysfunction: A meta-analysis and systematic review. *Neuropsychology reviews — In press*

**Lugtmeijer, S.**, Geerligs, L., De Leeuw, H. F., De Haan, E. H. F., Kessels, R. P. C., on behalf of The Visual Brain Group. Are visual working memory and episodic memory distinct processes? Insight from stroke patients by lesion-symptom mapping. — *Submitted*

**Lugtmeijer, S.***, Schneegans, S.*, Lammers, N. A., Geerligs, L., De Leeuw, F. E., De Haan, E. H. F., Bays, P. M., & Kessels, R. P. C.. Consequence of stroke for feature recall and binding in visual working memory. * shared authorship — *Submitted*

Lammers, N. A., **Lugtmeijer, S.**, De Haan, E. H. F., & Kessels, R. P. C.. Accelerated long term forgetting: The influence of a prolonged delay on sensitivity of memory assessment and metacognitive confidence in stroke patients and healthy controls. — *Submitted*

Van den Berg, N. S.*, Lammers, N. A.*, **Lugtmeijer, S.**, Smits, A. R., Pinto, Y., the visual brain group, and De Haan, E. H. F.. Mid-range visual half-field deficits after stroke;
uncharted territory with clinical implications. — *Submitted*

Van den Berg, N. S.*, Lammers, N. A.*, Smits, A. R., **Lugtmeijer, S.**, Pinto, Y., the visual brain group, and De Haan, E. H. F.. Mid-Range Visual Functions in relation to Higher-order Visual Functions after Stroke. — *Submitted*

## Research Data Management

This research followed the applicable laws and ethical guidelines. Research Data Management was conducted according to the FAIR principles. The paragraphs below specify in detail how this was achieved.

### Ethics
This thesis is based on the results of human studies, which were conducted in accordance with the principles of the Declaration of Helsinki. The Medical Ethics Review Committee Utrecht (METC-No. 2015.372) approved the conduct of these studies. The research in this thesis was supported by an ERC Advanced Grant (#339374) awarded to E. H. F. de Haan.

### Findable Accessible
Anonymized data (MRI and CRF) are available upon request a year after the completion of the project (01-07-2021, E.H.F.deHaan@uva.nl). Data is stored on a UvA server for the project FAB4V.

For chapters 2, 3, and 4 research data have also been stored on the DCC cluster. After finalization of the project data were removed from the cluster.

Informed consent was obtained on paper. The forms are archived in the investigator site file along with all METC documents. All response forms from the neuropsychological assessment are stored. Storage for data collected in Nijmegen is now in office B02.13 but will be moved to the new building. Data will be stored for 15 years (from 01-07-2021) and may then be destroyed.

### Interoperable, Reusable
The raw data are stored in their original form. In the SFTP folder, MRI data is in .dcm format. In the analyzing folder MRI data is safed as .nii. The neuropsychological data is stored on paper and scores will be exported from the electronical CRF and saved as pdf upon completion of the study. A description of the experimental setup can be found in published articles. Analyzing scripts in .m can be provided upon request (selmalugtmeijer89@hotmail.com). The used software including version numbers is specified.

### Privacy
The privacy of the participants in this thesis has been warranted using individual subject codes. The key is stored in the investigator site file (ISF) and is only accessible to members of the project who needed access to it because of their

role within the project. The key is stored separately from the research data and will remain in the ISF. Data in chapters 2, 3, 4 and 6 are identifiable in the CRF and MRI data in chapter 3 and 4 are not yet defaced, therefore all data can only be shared upon request and after anonymization.

## Donders Graduate School for Cognitive Neuroscience series

For a successful research Institute, it is vital to train the next generation of young scientists. To achieve this goal, the Donders Institute for Brain, Cognition and Behaviour established the Donders Graduate School for Cognitive Neuroscience (DGCN), which was officially recognised as a national graduate school in 2009. The Graduate School covers training at both Master's and PhD level and provides an excellent educational context fully aligned with the research programme of the Donders Institute.

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