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

Lugtmeijer, S.

Publication date
2020

Document Version
Other version

License
Other

Citation for published version (APA):
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 chapter 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).
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 (Souza & Skóra, 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
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
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
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 and 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 healthy 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.