Mechanisms underlying Rapid Forgetting in Health and Alzheimer's Disease



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A thesis submitted for the degree of

Doctor of Philosophy

Trinity Term 2021

This thesis is dedicated to Christiane and Klaus for their very generous support.

Acknowledgments

Firstly, I would like to thank the many volunteers that have contributed their time and effort to this thesis which would have not been possible without them. Even Oxford's most grim weather could not keep them from patiently sitting with me and running studies. Also, I thank the Friedrich-Ebert-Stiftung for their generous personal and financial support.

And then of course my deepest thanks go to Professors Masud Husain and Sanjay Manohar who not only were and are my role models but are such cool supervisors. It is thanks to their daily enthusiasm and inspiring work that I applied for this DPhil and it is thanks to their generosity, patience and support that I was able to do this DPhil. They gave me all the space I needed to even do the *craziest* of all experiments *tonight* and then sat with me to discuss how all those pieces would come together and broaden our understanding of working memory. Words cannot describe how cool these two researchers are with their passion and the best interest for the next generation in their heart. I am glad that for me finishing this DPhil does not mean finishing to work with them but rather, after writing up this thesis, means we have more time for future projects now!

Thank you to Raquel! It started out with those short walks from the lab to Co-op and now I fear I will have to visit the coach museum in Lisbon one day which you keep talking about so fondly since you became the sister, I did not even know I always wanted. Given the numerous things we have lived through and will probably live through in the future without despair, I might one day forgive you that you promised home-made lasagne but served BigMac in the end.

Lisa, my fellow German and Wolfsonian, lab bench neighbour and casual partygoer, I am glad you joined Raquel and me to form the three musketeers!

Fabio, I am so lucky Raquel came in a double pack. Besides all the support you gave Raquel and me, sometimes by just simply being patient while we kept talking about data and asked you to proof-read texts, I am happy we were able to watch some good old classical movies when Raquel was out of town.

I would also like to thank the “old” generation of DPhil students who inspired me when I first joined the lab as an intern and who I looked up to when I started as a DPhil student myself. Thank you Yuen, Kinan, Campbell, Laura and Edwin. And then of course thank you to the “new” generation of DPhil students, Youssuf, Sofia, Imran, Xin-You, Tanja and Bahaa who fought together with me in our daily struggles of DPhil life. Also, thank you to the very supportive postdocs in the lab: Pierre, Rob and Michele.

Thank you also to all the good souls in the lab who kept everything running, Liv, Annika, Shannon, Verena, Dan, Vicky and Ellie. Special thanks also go out to Emily who is as much of an awesome organizer as she is an awesome lab bench neighbour!

My thanks also go out to Nahid for not only joining for so many fruitful discussions but also for being one of those up-and-coming researchers one can naturally look up to. And then there is Sean of course who will probably understand when I say that he is eine richtig coole Socke and I hope I will have many more discussions with him in the future.

My special thanks obviously go out to my parents who always did whatever they could to allow me to live my dreams. Who would keep motivating me and kept giving me all the space I needed to grow and become the person I am today. None of this would have been possible without their continuous strong and unconditional support. My dearest thanks go to my grandparents who would proudly watch me take every step and would not stop asking so many details about everything I would do and think about. Though I wish you would still be here to watch me succeed, I am so happy about all the memories I have about you. Also, I would like to thank my friends, among these especially Anil, who would stay supportive and patient even when during the most intense times, my responses would take somewhat longer.

And thank you Eva for staying so patient, wise, a bit crazy and the uniquely wonderful person you are even during the most challenging times of this DPhil.

Abstract

Working memory is known to allow retaining and manipulation of information over short periods of time. It forms an essential part of cognitive processes and over the years different researchers came up with models trying to explain the mechanisms underlying how we hold onto important information. From a clinical perspective, it is even more essential to explore what underlies forgetting over such short periods of time given that patients presenting in the clinic with memory problems can suffer from transient innocuous to severe neurodegenerative disease associated with forgetting.

In a first chapter, classical and modern models of working memory are explored and mechanisms of guiding attention in working memory are introduced. Their implications and relationship to anatomical structures are discussed in order to set the scene for the following chapters in which their relevance for the detection of significant impairment due to neurodegeneration is tested. In particular, one domain of working memory, rarely explored in the past, is examined: Though previous studies on working memory focused on encoding and maintenance, only few researchers have yet looked into retrieval the literature on which is in particular explored in the introduction.

The following three empirical chapters explore in a total of nine experiments how retrieval cues impact on retrieval from visuospatial working memory, how retrieval of information already in a privileged state is protected from interference and finally how information retrieved from working memory can be tested in the

absence of a cue. This new uncued free full report allows for the distinction between errors that happen due to forgetting or confusion of one or several features of objects that are to be remembered.

In the second half of this thesis, essential findings in working memory come to be applied in patient populations. Firstly, the effects of rivastigmine on working memory performance and focussing attention are under investigation in people suffering from Parkinson's disease dementia. Secondly, a new gamified tablet-based task for the use in people at risk of developing Alzheimer's disease in the future is introduced and tested in different age groups

In conclusion, this thesis shows that retrieval cues themselves can impair retrieval from visuospatial short-term memory and that most recently presented information is protected from these detrimental effects. Moreover, one can test working memory in the absence of a probe which allows to assess the fate of all features bound into objects individually. Finally, rivastigmine is shown to improve working memory performance in patients suffering from Parkinson's disease dementia and different age groups perform similar in a portable tablet task that is aimed at detecting pathologic but not age-related changes in working memory.

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Acronyms

ACC Anterior cingulate cortex

AD Alzheimer's Disease

ApoE Apolipoprotein E

dlPFC dorsolateral Prefrontal Cortex

FAD Familial Alzheimer's Disease

HSV hue saturation value

LOAD late-onset Alzheimer's Disease

MPRAGE Magnetization Prepared - Rapid Gradient Echo

PD Parkinson's Disease

RGB red green blue

WAIC widely applicable information criterion

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1. Introduction

Memory functions are broad. Very intuitively, they include storage of information over time, be it just for short or for longer periods of time. However, memory also includes directing attention and selection of information to be stored. Moreover, concepts of memory also include manipulation of information held within the storage allowing for short- and long-term planning and cognitive control. The following introduction will show how our perception of memory has changed and developed continuously over time.

1.1 Different models of short-term memory and its neurological correlates

The computer this very thesis was written on largely relies on two different storage systems. That is a long-term storage on one hand and a short-term storage on the other. This separation also seems very natural for our very own human memory. Yet, this approach to human memory is relatively young. It was not until the 1960's that a monolithic concept of one memory storage would begin to crumble. With a new information processing approach to psychology, researchers started adapting the computer metaphor. The dominant multi-store model of the time suggested that external information came into a temporary sensory memory which was assumed to be part of perception per se and from there the information was passed on to a short-term memory which then passed on information to long-term memory. One such popular model was presented by Atkinson and Shiffrin

who assumed that the short-term store of information would also act as working memory (Atkinson & Shiffrin, 1968): A system for holding information while one processes their content, achieving a range of different tasks. Another assumption of this modal model was that information being held in this storage was guaranteed to be moved into a long-term storage (**Fig. 1.1**).

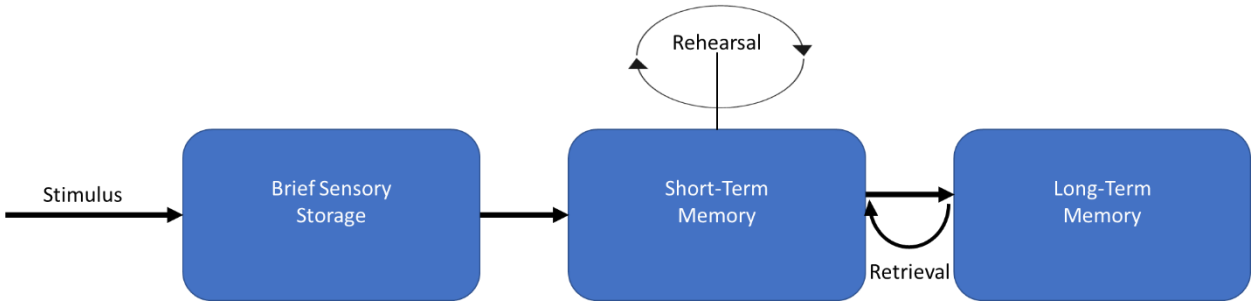


Figure 1.1 | Simplified Schematic of the Modal Model by Atkinson & Shiffrin (1968).

Notably, Atkinson and Shiffrin suggest that whatever information entered short-term memory would also go into the long-term storage. Soon the view that the duration of information being kept in short-term memory determined whether it was shifted into long-term memory would be criticised. Instead, Craik and Lockhart suggested that the degree and depth of encoding would rather determine whether information would be moved into the long-term storage.

However, the levels of processing model by Craik and Lockhart rather suggested that not the duration of keeping information within the short-term storage but rather the degree and depth of encoding would determine whether information is shifted to the long-term storage (Craik & Lockhart, 1972). Furthermore, a patient studied by Brenda Milner showed disrupted long-term memory with his deficits leading to trouble in the acquisition of new information. But on the other hand, he would show a normal degree of short-term memory function as measured in digit spans for example (Scoville & Milner, 1957).

A patient studied by Shallice and Warrington on the other hand was not able to remember sequences of numbers above two but would present with long-term memory that was comparable to that of controls (Shallice & Warrington, 1970). In conclusion, these cases suggest two separate and independent storage systems, however, the modal model does not seem to make a correct prediction about transfer of information into the long-term storage: If said information would have to go through short-term memory to enter the long-term system, a patient with impaired short-term memory would not be able to sufficiently use the long-term storage. Also, if the short-term storage was purely working memory, patients suffering from deficiency of the short-term system should not be capable of complex processes of thought which they were.

Here, two modern-day pioneers that would shape the world of working memory up to this day would come forward with a model of working memory that would criticise a view on short-term memory as a cognitive ability that would only be limited to storage as such. The two psychologists Alan Baddeley and Graham Hitch developed a new model of working memory that would see working memory as an instance of cognitive control (Baddeley & Hitch, 1974). Their model tried to explain how attention could be switched from one domain to another within split seconds. After developing this model, they recruited participants they would confront with digit spans. These were of increasing length in order to fill their short-term memory up to the point it would be full and unable to encode any further digits while they were to do cognitively demanding tasks. Notably, people

were still able to execute the cognitively demanding tasks while their short-term memory was supposedly filled to its capacity by the to-be-remembered digits of the digit span. Both pioneers concluded that something else than only a capacity-limited cognitive instance must be at work (Baddeley & Hitch, 1974).

Baddeley and Hitch proposed a model consisting of three components, at its centre the attentional system which they assumed was limited in capacity (**Fig. 1.2**). This central executive is aided by two subsystems, the first of which being the phonological loop which was assumed to hold verbal and sound information, like digit spans. This phonological loop is divided into two different subcategories. The phonological store on one hand is responsible for processing spoken words for short periods of time. The articulatory control process on the other hand can be seen as the inner voice and is responsible for the processing of speech production. The other subsystem holds visual and spatial information and is called the visuospatial sketchpad. These components are assumed to work together in a coherent way. Their model also allowed Baddeley and Hitch to come up with theories on how we forget. I.e., based on experiments that were meant to address the phonological loop, the authors found out that people were only able to remember as much as they were able to say within a short period of time and rehearsal was needed to keep this information. If they were to produce irrelevant sounds concurrently like ‘bla bla bla’ (termed “articulatory suppression”), the phonological information stored would suffer. This suggests two forms of decay: Decay over time and decay due to fading of memory traces (Baddeley, 2012).

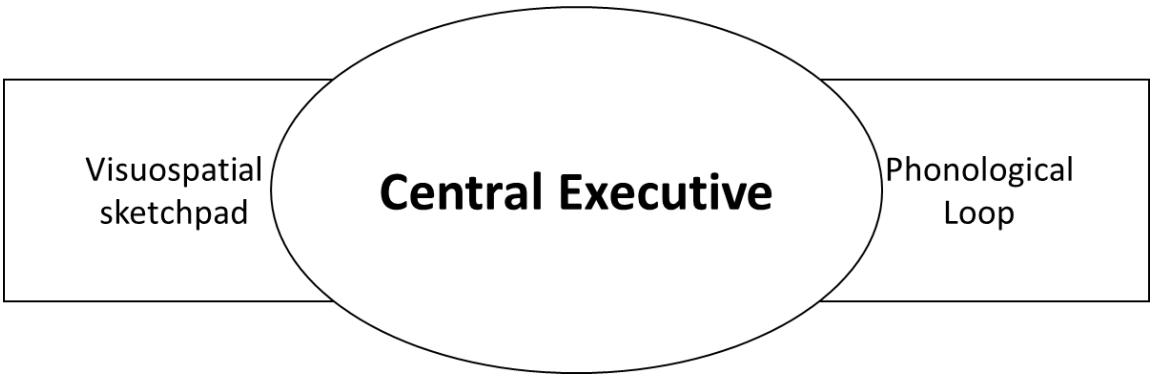


Figure 1.2 | Schematic of Baddeley and Hitch's working memory model. Baddeley and Hitch (1974) suggested a Central Executive at the centre of their working memory model. Two subsystems would support this central executive in its doing. The visuospatial sketchpad allows for virtual visualization and optical recall within one's mind. The phonological loop processes speech production, allows for rehearsal and stores verbal information. It is divided into the phonological store (speech perception, storage of spoken words over short periods of time) and the articulatory control process (inner voice, stores verbal information from the phonological store)

An often-cited example for the application of Baddeley and Hitch's model is window counting. I.e., if one was to count the windows of the flat or house one lives in, the information about this building would be moved into short-term memory. The windows would be virtually retrieved through the visual sketchpad. Counting would happen through the phonological loop as the inner voice. The central executive would coordinate between these different processes.

Another one of the big models in working memory is the one developed by Nelson Cowan (Cowan, 2016) who depicts short-term memory as the activated portion of long-term memory (Fig. 1.3). In this case, short-term memory is limited by a focus of attention. Like Baddeley and Hitch, Cowan assumed a central executive as well as sensory storage but in addition, long-term memory would be active in the

model and guide the focus of attention. This suggests that familiarity due to information being already involved in long-term memory plays an important role in keeping information over short periods of time. Also, the capacity of the focus of attention plays an important role. Cowan suggested the focus of attention to hold four chunks which may contain more than single items each. The most important difference between Baddeley and Hitch's model and Cowan's model is that the former see long-term memory as being an independent system from short-term memory though the two constantly interact with one another. Cowan, however, sees short-term memory as the activated fraction of long-term memory.

This difference already goes to show just how much disagreement there is on the interaction of long-term and short-term memory up to this day. Though it has been largely accepted since the 1960's that there are two different processes involved in memory, namely short- and long-term memory, the distinction between these two is yet to be further explored. More on this distinction will be discussed in the next subchapter.

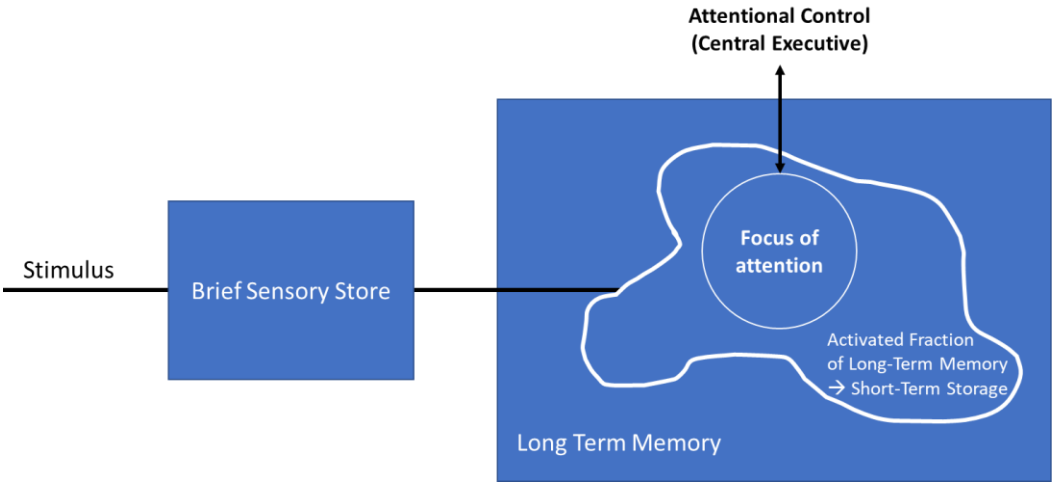


Figure 1.3 | Schematic of Cowan's Embedded Processing Model of Working Memory.

In Cowan's model, stimuli are processed by a sensory store holding this information over short periods of time. Shor-term memory itself is the activated fraction of long-term memory. The focus of attention guides the encoding and retrieval of processes.

The models described so far have shown interference, decay and capacity of focussing attention as potential sources of forgetting. Engle showed an additional potential source (Engle & Kane, 2003). In their studies, Engle and colleagues tested a large group of subjects for their working memory span. They show that a subgroup with a very high span also performed better than a group with a very low span in recall from episodic long-term memory, in generating information from semantic categories and in an antisaccade task due to reduced susceptibility to interference. Hence, the authors suggest inhibitory control to be essential to the understanding of working memory performance.

Newer models pick up on a more computational approach to memory. For example, Oberauer's model suggests six overall tasks completed by working memory (Oberauer, 2009):

1. maintaining structural representations by dynamic bindings,
2. manipulating structural representations,
3. flexible reconfiguration,
4. partial decoupling from long-term memory,
5. controlled retrieval from long-term memory, and
6. encoding of new structures into long-term memory

This approach also reflects a view of working memory that suggests activated long-term memory to be at least some part of it. Crucially, Oberauer emphasises another type of interference that is originated in the way memory is tested itself. Besides a declarative part of working memory, Oberauer suggests the existence of procedural working memory. Whereas an example for declarative load would be the digit span to remember, the procedural load could be seen as the task load of the memory task itself. This suggests that complicated task rules can themselves impact on participants' performance.

Another important distinction between Oberauer's and Cowan's model is that Oberauer introduces a one-element focus of attention that only holds one chunk at the same time. If a manipulation was to be made to a set of stimuli, Oberauer's model suggests that each of the input stimuli will be moved into this one-chunk focus one by one and then manipulated.

Moreover, some computational models also suggest an interference caused by the relationship between stimuli: Schurgin and colleagues (Schurgin et al., 2020) show that correct responses and supposed guessing can be fully explained by levels of psychophysical similarity in the stimuli presented. In their confusability competition model, the authors show that the similarity between target and foils can itself explain participants' performance by showing that higher degrees of similarity also lead to higher degrees of supposed guessing.

Work on visual short-term memory adds another important aspect to interference, namely binding. Luck & Vogel pioneered a series of simple visual short-term memory tasks that involve presentation of several different visual stimuli followed by the presentation of a probe (Luck & Vogel, 1997). Here, participants are to decide whether the probe was part of the previously presented memory array or not. The authors found participants' memory to be limited to four no matter whether one feature or several features per item were to be remembered. I.e., whether the shape (arrow, circle, square) of a stimulus was to be remembered only or whether the colour was also important to solve the task. This suggests that items are remembered independently of the number of features they consist of. Further research suggested that maintaining these bindings against interference is demanding and will result in poorer performance in tasks (Wheeler & Treisman, 2002).

1.2 Short-term memory and its relationship with long-term memory

Though the description of the models above has partly touched on the connection between short-term and long-term memory, the relationship between these two needs to be examined further.

In Baddeley and Hitch's model (Baddeley, 2012), the component most likely directly linked to long-term memory is the phonological loop which could, at least in part, be linked to lexical information stored in long-term memory and is most likely also based on more procedural language habits. I.e., for an English native who is not familiar with any other language, learning and rehearsing a list of English words is most likely easier than learning a list of German words over a short period of time.

Cowan has, of course, suggested working memory to be an activated form of long-term memory and directing the focus of attention is based on previous information stored within the latter (Cowan, 2016). As shown earlier, Oberauer's model (Oberauer, 2009) clearly points out the direct connection between short-term and long-term memory in points 4-6 of the concepts involved in working memory (4. partial decoupling from long-term memory, 5. controlled retrieval from long-term memory, and 6. encoding of new structures into long-term memory).

Coming back to Baddeley's model, he proposed that all information coming into short-term memory was processed by the subsystems that themselves are influenced by long-term memory (like the phonological loop is influenced by

lexical knowledge). Rehearsal of information will finally lead to information going over into long-term memory. This transition is especially supported the stronger the connection between new information and long-term memory. I.e., a poem rehearsed in the native language is easier to remember than a poem in a language never spoken or heard before.

1.3 Brain regions related to short-term memory

Given the growing interest in modelling short-term memory and great advances in neuroimaging, it is not surprising that different components of the most prominent models have been associated with different brain regions. In early single-unit recordings from monkey brains, Goldman-Rakic found continued cell activation in the frontal cortex to be correlated to successful recall of information whereas a disruption of this activation led to a higher degree of error (Goldman-Rakic, 1988). In particular, the dorsolateral pre-frontal cortex (dlPFC) has been linked to tasks with high demands of executive control. I.e., Kim and colleagues designed a task in which participants were to remember two numbers and their locations and then, during the delay, were to either add another number to the ones remembered or to virtually move the numbers' representation to a different screen location (C. Kim et al., 2015). It was in the most demanding condition in which they had to do both these operations that their performance correlated with the activation in the dlPFC.

In addition, the anterior cingulate cortex (ACC) has been identified as an important structure for guiding attention: Osaka and colleagues showed that dividing attention led to an increased activation of the ACC (Osaka et al., 2003). They asked participants to remember the first word of each of four sequentially presented sentences. After each sentence, they were also asked whether the presented sentence was semantically true or false. Thus, in this dual task, participants were to divide their attention, a process guided by the ACC.

In addition, Smith and Jonides argue in a review on neuroimaging analysis on working memory that patients with lesions to their right inferior posterior parietal area show selective impairment in spatial processing and spatial memory suggesting the importance of the right parietal cortex in tasks that involve spatial attention and memory (Smith & Jonides, 1998).

Components like the phonological loop and the visuospatial sketchpad are naturally linked to their corresponding perceptual brain regions. These are the Wernicke and Broca area for the phonological loop and the occipital cortex for the visuospatial sketchpad (A. Baddeley, 2012).

In summary, a network of frontal, parietal and sensory areas form the neural correlate of our short-term memory.

1.4 Sources of forgetting in short-term memory

How do people forget? Two opposing views have suggested that we forget because of passive decay over time or because there is interference between

items stored in memory. Recent evidence has demonstrated that both factors play a role in short-term memory (Pertzov et al., 2017). Classically, memory research has been based on documenting whether an individual remembers something or not – a binary, correct / incorrect index. However, Husain and colleagues (Bays & Husain, 2008; Mah et al., 2014) have developed new, continuous (analogue) response measures to probe memory where participants have to reproduce a feature of a remembered item (e.g. the orientation or location of a coloured bar that they saw in the memory array).

Using such sensitive methods, it was possible to track how people forget over just a few seconds (Pertzov et al., 2017). The more items people have to hold in STM, the faster the rate of decay, indexed by increasing error on the continuous response measure of memory (e.g., increase in angle of error in reporting the orientation of a coloured bar). In addition, the greater the number of items in memory, the more likely people are to "misbind" features that belong to different objects in short-term memory. Thus, if they are remembering a red horizontal bar and a blue vertical bar, they might report the orientation of the red bar when probed to reproduce the orientation of the blue one. In other words, their memories are corrupted by other items held in memory (Pertzov et al., 2017).

This methodology has also allowed researchers to model the sources of error in people's recall: in terms of how much of their error might be attributed to misbinding, as opposed to increasing noise in representations, or random all-or-nothing corruption (Bays & Husain, 2008; Mah et al., 2014).

Bays and Husain presented a model that allows to distinguish these three sources of error in recall from short-term memory. According to this model, participants' performance either suffers from error due to misbinding, due to corruption from random noise (guessing) or due to the increased noisiness of remembered representations (imprecision). Bays and Husain (2008) used a von-Mises distribution (**Fig. 1.4**), a circular version of the Gaussian distribution, which they centred around the target shape, or around one of the distractors (misbinding). In the case of misbinding, a participant remembers all information presented but is not able to correctly bind features belonging together in an object. Guessing is represented by a uniform distribution spread across the whole circular space.

Results collected from short-term memory tasks are not only amenable to such purely behavioural models but also to neural network modelling and to electrophysiological recordings. Some of these models have proposed that representations in memory are maintained by recurrent feedback loops in neurons (Compte, Brunel, Goldman-Rakic & Wang, 2000; Wang, 1999). I.e., information in these models would reverberate in neural populations (Deco et al., 2008). These sustained or oscillating electrical activations in neural models can be recorded during the retention interval (Doesburg et al., 2011; X. Yu et al., 2017).

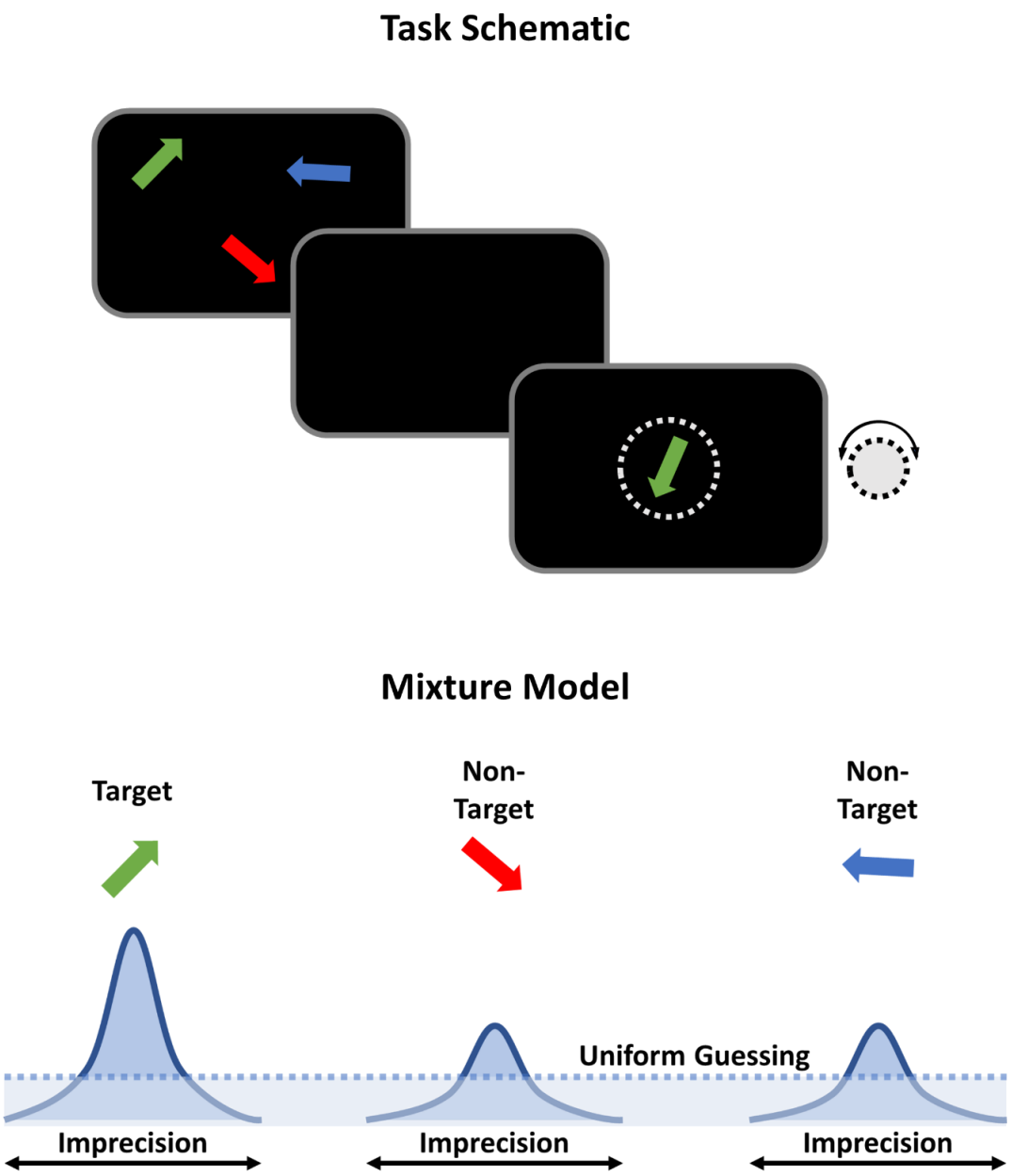


Figure 1.4 | Mixture model of error sources in tasks with continuous response space. The top depicts the task schematic of a typical reproduction task with a continuous response space. Here, participants are presented with three arrows the colours and orientations of which they are asked to remember. After a delay, they are to reorientate one of the three arrows, in this case the green one to match the original orientation. In the mixture model, participants either solve this task given they remember the orientation at test correctly or they make mistakes of different types as depicted at the bottom. I.e., their response either follows a circular von-Mises-distribution around the target or one of the non-targets or is drawn from a random distribution around the circular space. If the response is drawn from a von-Mises distribution, the distribution's width represents participants' imprecision.

However, to keep representations of several different items from collapsing into indistinguishable single representations, one theory suggests that neurons representing a single item might be linked together into a synchronously firing assembly of cells (i.e., Jensen & Lisman, 1998). While synchronization between neurons representing features that belong to the same item maintain – or bind – an item's information, asynchronization between different cell assemblies may prevent interference between information belonging to different items (Raffone & Wolters, 2001). According to this model, disruption of such mechanisms might interfere with precise timing of excitatory neurons (Singer, 2009). These approaches found their way into short-term memory research as well: The Singer group proposed that "prefrontal oscillatory activity may be instrumental for the dynamical integration of local and global neuronal processes underlying short-term memory" (Pipa et al., 2009).

The most recently encoded items show electric activity leading to an attended or "focused" state which allows the item in that state to be remembered with greater fidelity (more precisely) than others (Zokaei, Ning, et al., 2014). Previously encoded items, however, can be concurrently held in memory but crucially in the background, encoded in activity-silent synaptic traces. This dual functional structure provides an explanation for a range of perplexing attention and memory effects in behavioural experiments that has hitherto been difficult to understand with a single theoretical framework.

Some neural models predict several limitations to the capacity of short-term memory (i.e., Manohar et al., 2019). Electric activity in cells or cell assemblies

passively decays over time and thus information maintained would be lost. The maximum number of items maintainable is subject to the resources needed to encode and keep information at different levels of synaptic or electrical activation while keeping them from decaying over time. At the same time, the correct binding of features to a unified object is crucial in this process. A very interesting question that arises is: With increasing neural disruption – as observed in neurodegeneration – what is the effect on how information is encoded, maintained or retrieved? Are there differential effects on these processes? And how can these processes be tested in modern-day memory tasks?

1.5 The modern visual short-term memory task

Ever since Baddeley used tasks to test his hypotheses, such as the digit span, short-term memory tasks have come a very long way and these days are very often run on computers or tablet computers. Usually, these visual short-term memory experiments are designed to present participants with a set of items such as arrows of different colours and orientations or coloured patches in different screen-locations (arrows: Tabi et al., 2019; coloured patches: Luck & Vogel, 1997, bar orientations: Pertzov et al., 2013, shapes: Liang et al., 2016, vowels: Joseph et al., 2015). Participants are asked to keep the features of this "memory array" in mind and are told that they will be asked to remember certain ones of the features (**Fig. 1.5**). This visual memory array is followed by a memory delay in form of a

blank screen. During this delay, participants need to maintain the information stored before. At the last stage of the experiment, participants' memory for the visual features is tested using a probe.

In change detection tasks, participants usually must determine whether the probe is the same or different from the target. In addition, some tasks require them to determine the direction or quantity of change between probe and target (Luck & Vogel, 1997). In reproduction tasks, on the other hand, participants are required to reproduce one or more features of the target (i.e., Pertzov et al., 2017). In the example of memory arrays consisting of arrows, participants would be presented with an arrow shown in the colour of one of the items of the memory array. Volunteers could be asked to point that probe arrow into the direction they think it pointed at beforehand.

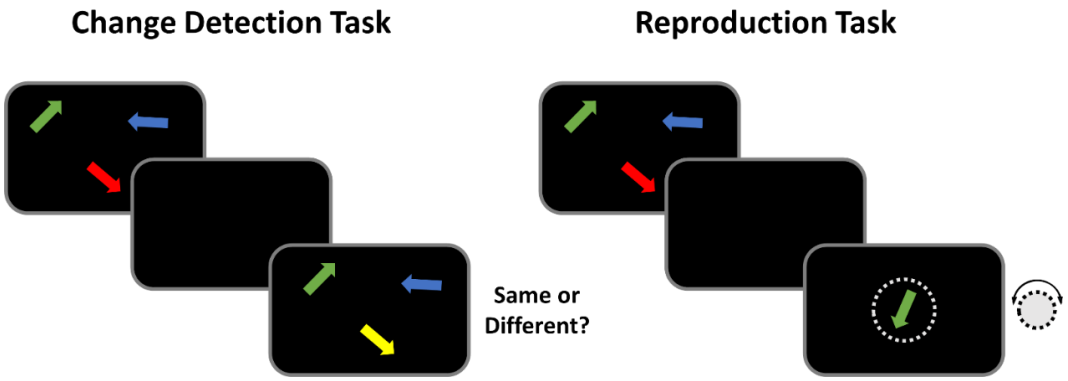


Figure 1.5 | Schematics of Change Detection versus Reproduction Tasks. The schematic on the left depicts a change detection task in which participants are asked to remember a set of three arrows. After a short delay, they are presented with another set of arrows and asked whether this probe set is identical or different to the initial set presented. In a reproduction task, as presented on the right, participants are also presented with a set of arrows, however, after a short delay, they are asked to reproduce the orientation of one of these using a dial.

This seemingly simple procedure requires participants' memory to perform three consecutive tasks: 1) Encode the memoranda, 2) Maintain the memoranda and 3) Retrieve the memoranda. In the following, different streams of research in this field will be presented (**Fig. 1.6**).

Encoding

One of the most common ways to manipulate demands at the stage of encoding are pre-cues. That is, the encoding display is accompanied by additional features that will point towards more relevant information that is likely to be probed (Jost et al., 2011; Vogel et al., 2005). One example is an arrow that points towards the information that is more likely to be probed than the information no arrow points towards. These spatial cues might allow to selectively encode fewer information and thus increase performance by allocation of resources to the items that are more likely to be probed.

A great advantage of studies looking at encoding is how efficiently they can be linked to imaging data. With the help of MEG recordings, the moments of visual reception, perception and oscillations that correlate with representations of stored memories, can be deciphered. As Roux and Uhlhaas (Roux & Uhlhaas, 2014) suggested, theta-band oscillations correlate with organization of sequentially ordered short-term memory items. Especially in sequential encoding, there has been a decade-long interest in identifying the underlying mechanisms of encoding:

What was the right phone number again? Sequences play an important role in our daily life and yet the exact mechanisms of storing, maintaining and retrieving sequential information have been up for discussion for decades (Conrad, 1965; Solway et al., 2012). Over the course of this debate, different models of sequential storage have been established. The simplest is termed "associative chaining": Pairs of successive items of a sequence are stored together, thus moving back (or possibly forward) in the sequence works through processes of association between the different items (Solway et al., 2012). A more cellular approach is a model of neurons that selectively activate according to sequential position. This has been found to be true for monkeys, rats and humans (Berdyyeva & Olson, 2016; Kalm & Norris, 2017; Place et al., 2016).

One region that seems to especially deal with sequential information is the hippocampus in which neurons tend to activate sequentially (King & Dehaene, 2017; Kurth-Nelson et al., 2016; Wang et al., 2016). The majority of studies concerning the involvement of the hippocampus in storing sequential information, however, has been conducted in long-term memory.

Despite the overall debate about the exact mechanisms underlying memory of sequences, two effects, namely the primacy and recency effect, have long been established (Hurlstone et al., 2014). These effects suggest that some items in a sequence, the first and last, are prioritized over the other items of the sequence. They are recalled more precisely than other items and it has been concluded that

therefore they might be in a more ready state, such as, i.e., the focus of attention (Lewis-Peacock et al., 2012; Manohar et al., 2019; Zokaei, Manohar, et al., 2014).

Maintenance

Very similarly to encoding, manipulations during the maintenance interval can rely on cues. In this case, retro-cues point towards items that are more likely to be probed during the retrieval phase of the experiment (Griffin & Nobre, 2003; Landman et al., 2003; Souza & Oberauer, 2016). Another possible manipulation during the maintenance interval is the presentation of foils that are to be ignored (Fallon et al., 2018; Souza et al., 2014; van Moorselaar, Olivers, et al., 2015; Williams et al., 2013). Thus, the task is to remember only the originally encoded information and to protect it from the interferingly presented foils. The neuronal cell model (Engel et al., 1997) relies on synchronously firing neurons that bind features together into objects and keeps them from collapsing into single indistinguishable representations by asynchronization between different groups of neurons. Maybe misbinding occurs when groups of synchronously and asynchronously firing neurons are fed with new information while trying to maintain information that was already stored.

Further, there is evidence that the duration of the delay before participants are allowed to make a response has a significant effect on their ability to memorize locations driven by an increased imprecision (Cuthbert & Standage, 2018). Hence, delay duration is another factor that needs to be considered in terms of interference.

Retrieval

Surprisingly, little research has been conducted on how we retrieve information. In past theories of retrieval, authors have argued that a probe triggers retrieval of information through re-activation of features of the corresponding item in short-term memory (Farrell & Stephan, 2002; Sandberg et al., 2003). However, one (or more) of the items in memory might already be in a more ready, responsive state – in the focus of attention (Zokaei, Ning, et al., 2014). Presumably if this is the case, those items that are not in the focus of attention need to be re-activated by the probe for participants to respond correctly. Thus, only items that are not in the focus of attention should be susceptible to the effects described in the experiments above.

On a neural level, retrieval has been linked to the hippocampus, in particular to its subregion Cornu Ammonis 3 (Guzowski et al., 2004; Rolls, 2016): The mechanism associated to the process of retrieval here is pattern completion whereby a partial cue is able to reactivate the rest of the object it belongs to (Norman & O'Reilly, 2003). The Cornu Ammonis 3 plays an essential part in this on the neuronal cell level: After it receives input from neighbouring brain regions like the dentate gyrus and the entorhinal cortex in a pattern-separated manner, recurrent collaterals within the Cornu Ammonis 3 allow for recall of conjunctions between different inputs stored (Guzowski, Knierim, & Moser, 2004; Rolls, 2016). Thus, one part of an object allows for retrieval of all the information linked to it.

Despite the existence of such detailed neural models of retrieval and a great number of studies on retrieval from long-term memory, studies on retrieval from short-term memory are relatively sparse. Yet, the fact that retrieval can be linked to the hippocampus makes it interesting for the early detection of neurodegenerative disease that involve the hippocampus as detailed in the following chapters.

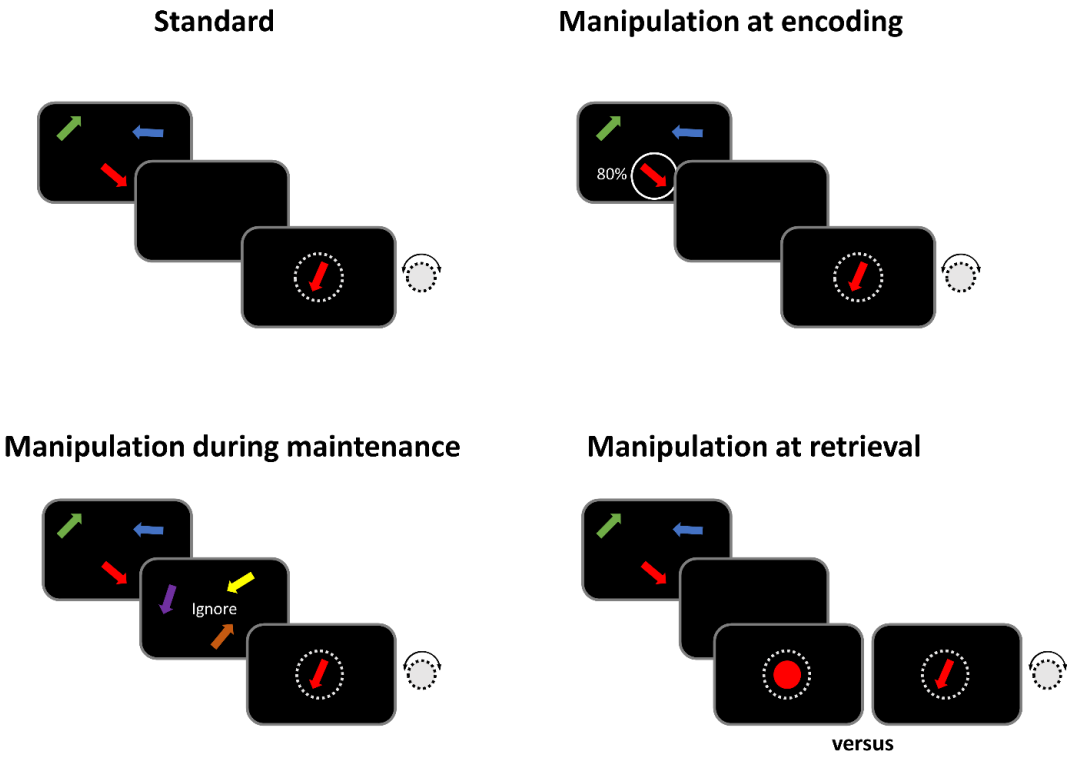


Figure 1.6 | Schematic of manipulations of encoding, maintenance, and retrieval in short-term memory tasks. The top left depicts the standard reproduction task underlying each of these manipulations. Here, participants are presented with a set of three arrows the orientations and colours of each they are asked to remember. After a short delay, one of the three arrows is presented on the screen and participants use a dial in order to reproduce the orientation originally seen. In the top right, a cue is presented together with the encoding display as a manipulation at encoding. Here, the cue suggests that there is an 80% chance that the red arrow will be probed as opposed to the blue or green arrow. In the bottom left experimental setting, participants are asked to ignore additional information during the maintenance interval as a manipulation during maintenance. Finally, the experiment at the bottom right shows a manipulation at retrieval. Here, participants are either probed with an arrow starting off at a random orientation or with a colour holding no orientation information.

Very recent evidence suggests that manipulations during these different phases (encoding, maintenance and retrieval) is not correlated. I.e., Tabi, Maio and colleagues (Tabi et al., 2021) manipulated processing demands during each of these stages: They asked participants to ignore items during encoding and maintenance and manipulated the degree of familiarity between probes at retrieval. Though each of their manipulations showed to be effective on participants' performance, they were able to show that none of the effects correlated between stages. They, thus, concluded that attentional directing during encoding, maintenance and retrieval was not a monolithic mechanism but rather consists of independent mechanisms guiding attention self-sufficiently.

Yet, to understand how this is possible, another mechanism underlying short-term memory requires further introduction.

1.6 The focus of attention

As several phenomena described in the text so far point out, some items in memory are prioritized over others. Prioritizing certain items within working memory over others is necessary for quickly switching between tasks which is a requirement in order to deal with the hustles and bustles of daily life (**Fig. 1.7**).

An item in such focus of attention is known to be recalled faster and with more precision, potentially because it is already active and in a response-ready state (Lewis-Peacock et al., 2012; Myers et al., 2017; Wolff et al., 2017; Zokaei, Manohar, et al., 2014; Zokaei, Ning, et al., 2014) and therefore protected against

interference which is the most common cause of forgetting (Oberauer & Lin, 2017). Such interference can be caused by an increasing number of items to be held in WM or duration of maintenance (Pertzov et al., 2017), by subsequent items that have to be ignored (Hu et al., 2016) or by the recall cue stimulus used at probe itself (Souza et al., 2014; Tabi et al., 2019). Yet, there is a lot of discussion on how exactly items are moved into this "focus of attention".

There are two opposing views on how items are moved into this focus of attention. On one side, some authors argue that a last item in a sequence remains in an active state (McElree, 2006; McElree & Dosher, 1989). Evidence for this hypothesis is provided by the last item in the sequence commonly being retrieved more accurately than preceding items. On the opposing side, it has been argued that the last items benefit only reflects a continuous curve of working memory capacity with the last item at one extreme (Donkin & Nosofsky, 2012).

These authors propose that retro-cues would protect items against visual interference, make them more accessible and be remembered more accurately (Souza & Oberauer, 2016). A retro-cue thereby is a cue that is shown in the retention interval of a visual short-term memory task. This retro-cue does not provide participants with any (additional) information about any of the memoranda but rather helps retrieve a previously shown object through reactivation of one of its features (i.e. an arrow points towards the location of one of the previously presented items). If an item was retro-cued in such way, it is usually retrieved more actively, and it has therefore been argued in previous

studies, that these items are stored in the focus of attention (Griffin & Nobre, 2003; LaRocque et al., 2014; Souza & Oberauer, 2016; Zokaei, Ning, et al., 2014).

Both views presented support the mechanisms underlying retro-cueing and recency to be independent of each other. Thus, an item that is presented last in the sequence (recency) should not benefit from being retro-cued. Finally, an experiment that uses both, recency and retro-cueing, should find these two effects to be additive but not interacting.

In a set of three well designed experiments, Niklaus, Singmann and Oberauer (Niklaus et al., 2019) provide evidence for this hypothesis. In a response-deadline paradigm, they measured speed-accuracy-trade-off for retrieval dynamics in a short-term recognition task. In a first experiment, participants were sequentially presented with a list of six words. After a delay, they were asked to indicate whether a centrally presented word was part of the sequence seen before. One half of the trials included a central retro-cue in form of an arrow that pointed towards the word that would be probed. Immediately when a response signal was presented, participants were asked to give a recognition response. Time between the probe and response signal was varied over trials, thus allowing to measure accuracy as a function of time over the retrieval time course. In a second and third experiment, Niklaus et al. first reduced the number of items presented, varied the delay between probe and response signal and finally presented colours instead of words, in order to generalize their results. In all three experiments, the retro-cue benefitted the first items in the sequence equally well as the final one. There was

no interaction of recency and retro-cueing, suggesting that both effects are additive.

These findings are in line with previous studies that show that retro-cues allow participants to retrieve information in absence of interference caused by a visual cue and thus more precisely (Souza & Oberauer, 2016; van Moorselaar, Olivers, et al., 2015). On the other side, it has been shown that adding additional visual information after a last item in the sequence finds the latter lose its recency benefit (Hu et al., 2016). With interference being a crucial cause of forgetting in visual short-term memory, an item that is protected from such disturbance should be retrieved more accurately, even in presence of an interfering probe.

For the thesis presented here, a focus of attention is assumed that will only fit one item at a time. In particular, it is hypothesised that recency AND retro-cueing will lead to an item being moved into the focus of attention. Importantly, *among* information encoded in activity-silent synaptic traces, some items might be recalled more precisely than others.

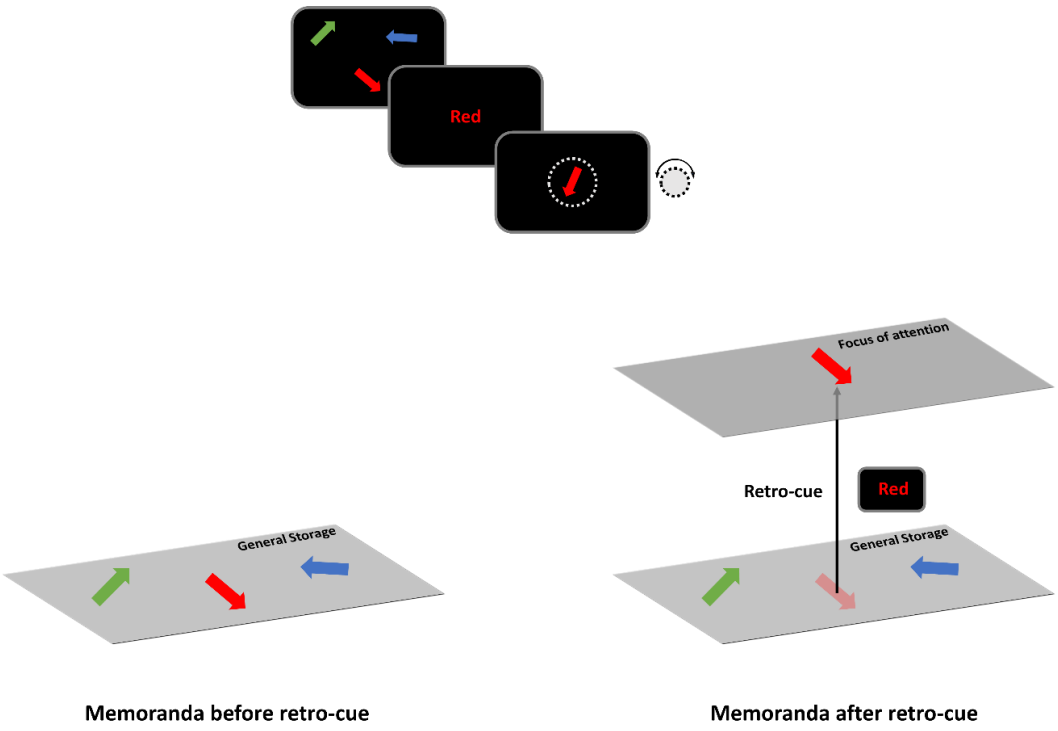


Figure 1.7 | Schematic of the focus of attention. The top schematic shows an experiment in which three arrows are presented. These are stored in short-term memory's General Storage (bottom left). Following a retro-cue, in this case the word *Red*, one of the items is moved into the focus of attention where it is more readily available compared to the other items stored in memory (bottom right).

1.7 Focus of attention in neurodegeneration

Patients with neurodegeneration such as Parkinson (PD) and Alzheimer's disease (AD) (Verbaan et al., 2007; Zokaei et al., 2020), present significant WM deficits. The implementation of sensitive delayed-reproduction tasks has allowed for the underlying mechanisms of these deficits to be investigated by dissociating the types of errors contributing to the memory impairment. While PD has been associated with increased number of random guessing, AD have been shown to have increased misbinding (Zokaei & Husain, 2019). In this thesis, I extend on this work by investigating patients with PD dementia and AD.

With different approaches towards the focus of attention established, there is another pressing open question. Does neurodegenerative disease affect the focus of attention in particular or short-term memory, including the focus of attention, in general?

One such disease that is known to be related to a general attentional deficit is Parkinson's Disease dementia. PD is a chronic and progressive brain disorder causing motor symptoms such as muscle rigidity, postural unbalance, tremor or bradykinesia, (Postuma et al., 2015) but also cognitive decline (Gratwicke et al., 2015; Kehagia et al., 2010). Despite being associated with a gradual depletion of nigrostriatal and mesocortical dopamine, other neurotransmitter systems such as the cholinergic, serotonergic and noradrenergic systems are also affected (Dubois et al., 1983; Kish et al., 2008; Zarow et al., 2003). Indeed, a common finding in

patients suffering from this type of cognitive decline is a cholinergic deficit across the cortex (Bohnen & Albin, 2011) with acetylcholine being a prominent neurotransmitter within the cortex, especially involved in attention. Thus, medication with cholinesterase inhibitors, that indirectly increase levels of acetylcholine, is assumed to improve patients' attention (Lawrence & Sahakian, 1998; Silver et al., 2008; Wesnes et al., 2005). Despite the fact that attention is generally increased in acetylcholine, leading to unspecific effects like a decrease of reaction time variability (Wesnes et al., 2005), it remains unclear whether specific aspects of attention, such as the stability of the focus of attention, are in particular affected. Here, the more general question is therefore whether and how much general visual attention is related to specific domains of visual short-term memory, such as the focus of attention.

Previous work might in fact contradict positive effects of medical treatment with cholinesterase: I.e., Bentley suggests that cholinesterase inhibition might interfere with retrieving information from short-term memory (Bentley, 2011). That might be because retrieval through pattern completion has rather been related to lower levels of acetylcholine (Decker & Duncan, 2020). Thus, low levels of acetylcholine might in fact re-establish the cortical state at the time of encoding which could, intuitively, be essential for pattern completion (O'Reilly & McClelland, 1994). An artificial cortical increase of acetylcholine might therefore rather impair retrieval and, thus, could have negative effects on short-term memory.

The answer to these two open questions, whether increased levels of visual attention relate to a more stable focus of attention and whether acetylcholine is

related to better or worse retrieval from visual short-term memory, will contribute to the overall understanding of how medical treatment can or cannot improve short-term memory deficits.

In addition to the actual treatment of short-term memory deficits in neurodegeneration, early detection and prevention is another emerging field in clinical short-term memory research. Yet, reliable measures that can be used at scale are still to be established.

1.8 Earlier detection of Alzheimer's Disease

With an aging society, memory deficits become a more and more common symptom in patients presenting in clinics. The possible origin of these memory problems can derive from a change of mood to progressing cognitive degeneration such as found in different forms of dementia. Thus, because cognitive impairment in neurological diseases has no on-to-one mapping, i.e., one disease can have a multitude of manifestations while different pathologies can be related with the same cognitive phenotype, they are challenging to detect.

This results in the importance of detecting the underlying aetiology of the deficit at hand as soon as possible. Hitherto established cognitive tests often lack the sufficient sensitivity to detect subtle cognitive changes underlying severe disease and very often, these tests need to be conducted in person, by trained personnel in a clinical setting. Together with a growing incidence of severe cognitive decline at later age, the factors demonstrated here show the need to establish a task that can detect cognitive changes typical for Alzheimer's disease early on while being largely available without previous training.

AD dementia comprehends the cognitive plus functional impairment in everyday life (McKhann et al., 2011). It starts long before a clinical diagnosis is made (Bateman et al., 2012; Kalia & Lang, 2015) or even shrinkage of the hippocampus (Bateman et al., 2012) started. It is characterized by the deposition of amyloid in specific regions of the neocortex, then spreading to larger amounts of the brain

(Braak et al., 1993). Also, tau deposition starts in the MTL and the locus coeruleus before extending throughout the entirety of the brain (Braak et al., 1993).

In order to detect this disease early on, a lot of research has been conducted on biomarkers: clinical, imaging, pathological, biochemical or genetic markers. For example, the apolipoprotein-E ε4 allele gene (APOE4) has been found to increase the risk of developing AD (Bateman et al., 2012). It is important to note, however, that most work has focused on the prodromal phase of the illness, closer to the diagnostic stage, which is when cognition begins to significantly decline. But what is important is to investigate this at the preclinical phase because that is when intervention will be more effective.

The development of novel cognitive tests may help in this endeavour as they have been shown to be more sensitive than the ones traditionally used in clinic (Zokaei & Husain, 2019). These delayed reproduction tasks are not just useful to examine the underlying mechanisms of WM in healthy people but also spot memory decline in aging. Additionally, they can be dispensed to many people online.

Most studies of memory in AD have focused on longer-term, episodic memory (Aggleton & Brown, 2006; Eichenbaum et al., 2007). However, Liang et al. have studied rapid forgetting of items held in short-term in rare cases with familial Alzheimer's disease with genetic mutation (Liang et al., 2016). Using this analogue response paradigm, they show that misbinding occurs at a significantly higher rate than in controls in both pre-symptomatic and symptomatic individuals with the

familial AD gene (FAD), despite not yet exhibiting cognitive deficits on standard neuropsychological tests. Moreover, misbinding rates were higher in cases with smaller hippocampi. Taken together with data from focal medial temporal lobe patients on the same paradigm (Pertzov et al., 2013), these data suggest that pathological misbinding might be an important cognitive signature of hippocampal dysfunction. Furthermore, it might potentially be a key pre-symptomatic marker for sporadic, late-onset Alzheimer's disease which is far more common than in familial Alzheimer's disease.

In an analogue response short-term memory task developed for a tablet computer, forgetting and mechanisms underlying it can be measured in late-onset Alzheimer's disease and groups at high risk of developing AD. These groups are in particular:

1) Mild cognitive impairment: people who have cognitive impairment but do not fulfil the criteria for dementia have a 10% annual risk of converting to LOAD (Petersen et al., 1999).
2) ApolipoproteinE ε4 (ApoE ε4) genotype positive heathy people: the highest known genetic risk factor for developing LOAD (Heise et al., 2014; Liu et al., 2013).

Especially when using a task version that is gamified and largely available, larger datasets can be collected, and average performance for different age groups can be recorded. Thus, a task like this has the potential to be a powerful screening tool for people with hippocampal dysfunction such as seen already in early or pre-symptomatic stages of Alzheimer's disease.

In the five empirical chapters of this thesis light will be shed on the topics and open questions introduced in this first general introduction.

1.9 Thesis outlook

In a first empirical chapter, this thesis explores the pattern-completion approach towards retrieval of information from visual short-term memory using a set of three experiments in which the probe itself can either be presented with or without additional interfering information. Without additional information presented in the probe, pattern completion should work more sufficiently compared to when the probe holds additional information that is not required to solve the task at hand. This might, however, only be the case if the information probed is not yet in the focus of attention. Once information is in the focus of attention, it should not matter whether the probe holds additional information. These three experiments were published in Tabi et al., 2019.

Following up on the results of the first chapter, a second chapter goes to explore how exactly information is moved into the focus of attention and how recency and retro-cueing are different in protecting information from probe interference. This series of 4 experiments is in the process of being submitted for publication by the time this thesis is being submitted.

A third chapter concludes this thesis' train of research on retrieval. Here, a new format of testing short-term memory is introduced that does not require a physical probe but rather allows for direct reproduction of remembered information. This chapter directly compares this new method of uncued probing with the standard pattern-completion approach. These two experiments were presented at VSS (Tabi et al., 2020).

The fourth chapter explores how the focus of attention is affected in clinical disease, such as in Parkinson's disease dementia and how drugs used in treatment of dementia, i.e. an acetylcholinesterase inhibitor, have an impact on stabilizing patients' focus of attention.

Finally, the last empirical chapter looks into scaling up previous findings that link misbinding as a dysfunction of the hippocampus to early detection of Alzheimer's disease in which the hippocampus is, very often, the first region to be affected. Parts of the dataset have been presented at the International Brain Research Organisation conference in 2019 (Tabi, Eriksen et al., 2019).

2. Recall cues interfere with retrieval from visuospatial working memory[1]

2.1 Abstract

Visuospatial working memory allows us to hold multiple visual objects over short delays. It is typically tested by presenting an array of objects, then after a delay showing a "probe" indicating which memory item to recall or reproduce by adjusting a target feature. However, recent studies demonstrate that information at the time of probe can disrupt recall. Here in three experiments we test whether traditional memory probes, which contain features that compete with the feature to be recalled, may themselves interfere with performance. We asked participants to report the direction of one of several coloured arrows in memory, based on its colour. First, we demonstrate that recall is better when the probe is initially just a coloured dot, rather than a coloured arrow which has to be adjusted to match orientation memory, consistent with interference from features of the probe itself. Second, this interference is present even when a mask follows the memory array, suggesting that the interference does not work by degrading immediate or iconic memory. Finally, when items are shown sequentially, the first and last items are invulnerable to probe interference. Our findings support recent theories of

[1] This chapter, including all texts and graphs, has previously been published in Tabi, Y.A., Husain, M. and Manohar, S.G. (2019), Recall cues interfere with retrieval from visuospatial working memory. Br J Psychol, 110: 288-305. https://doi.org/10.1111/bjop.12374 under the terms of the Creative Commons CC BY license.

associative recall, in which probes re-activate features in WM, retrieving information by pattern completion.

2.2 Introduction

Interference is considered to be a crucial cause of forgetting in working memory (Oberauer & Lin, 2017). For example, recall errors can be biased towards reporting the features of other items held in memory, an effect that increases with the number of items that are encoded into working memory and duration of maintenance (Pertzov et al., 2017). A further intriguing possibility is that interference could arise at the time of the retrieval due to the probe used to cue recall.

In many WM studies, the probe which is used at retrieval often contains attributes that might interfere with the feature that has to be recalled. For example, in adjustment paradigms in which participants are asked to report the direction of an arrow, the probe is usually an arrow the direction of which must be subsequently adjusted to match the memory of its orientation (Gorgoraptis et al., 2011; Pertzov et al., 2017; Zokaei, Heider, et al., 2014). In principle, this arrow could itself interfere with stored items, since it holds information of a similar type. The probe may therefore introduce additional information over and above the stored memory array that could interfere with memory recall.

One demonstration that information presented at test interferes with memory retrieval comes from the retro-cue effect (see Souza & Oberauer, 2016for a review). In the retro-cue paradigm, a cue (usually an arrow) is shown during the retention interval indicating the location of the item that will be tested at the end

of the trial. The retro-cue provides no information about the memorandum's feature or about the response, thereby only allowing participants to retrieve information from memory using the location associated with the item. Performance in retro-cue trials is better than performance in trials in which memory is tested directly (i.e., no-cue trials).

One explanation of this effect is that retro-cues allow participants to retrieve information in the absence of the interference inflicted by the memory probe. To provide evidence for this hypothesis, Souza et al., 2016 included a condition in which the probe was shown at the same time as the retro-cue, but participants had to delay making a decision to the probe. In this new probe + delay condition, the probe could interfere with memory retrieval, but participants were still forced to invest more time in retrieving information from memory as in the retro-cue condition. Although the probe + delay condition also improved accuracy compared to the no-cue condition, this effect was smaller than in the retro-cue condition, indicating that one component of the retro-cue benefit is protection from probe interference. Protection from interference was also demonstrated in a task in which participants had to reproduce the memorandum's feature (i.e., colour) in a continuous scale by using a colour wheel. Souza, Rerko, and Oberauer (2016) observed that part of the erroneous responses in this task were due to an increased probability of selecting colours in the colour wheel that appeared next to the probed location (a colour wheel attraction effect). This attraction effect was extinguished in the retro-cue condition which delayed the presentation of the

colour wheel until retrieval of the probed item was already substantially advanced. In line with the idea that the colour wheel interferes with memory retrieval, replacing the coloured wheel by a grey wheel led to an overall improvement in performance even in the absence of a retro-cue, and likewise removing this source of interference also reduced the retro-cue benefit.

Can a common mechanism explain why probes interfere with recall, but also why retro-cues confer an advantage even if they result in increased delays? An associative pattern completion mechanism (**Fig. 2.1**) would predict that the relevant feature of the probe triggers re-activation of the other features belonging to the appropriate item in memory, allowing them to be recalled (Manohar et al., 2019). Crucially this process of pattern completion would be expected to be disrupted if the probe also activated a competing feature on the dimension to be recalled, that was not actually in the object being recalled. In this way, the presence of an additional irrelevant perceptual feature might act as an obstacle to retrieval. Thus, the additional feature is predicted to interfere with associative retrieval.

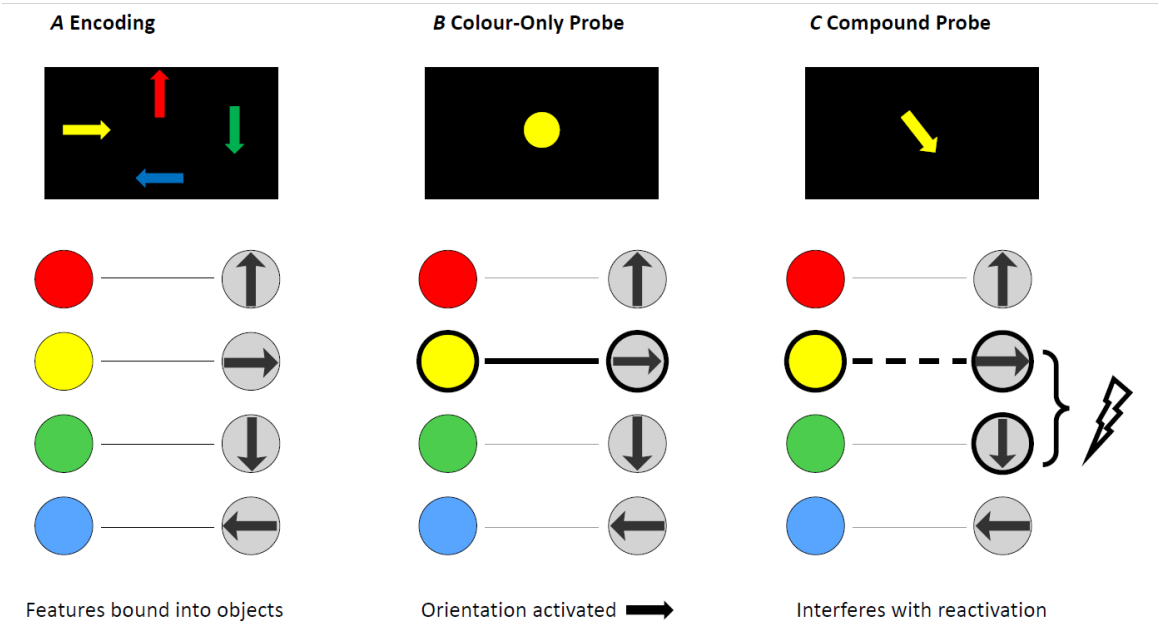


Figure 2.1 | Schematic of pattern completion with a colour-only versus a compound probe. **(A)** When participants are presented with a memory array and are asked to keep the items' colours and orientations in mind, they encode both dimensions for each item and bind them together into objects. After a memory delay, participants are presented with a either colour-only probe that only holds information on one dimension or compound probe that holds information on two dimensions. **(B)** In case of the colour-only probe, this colour cue can reactivate the corresponding orientation information, by pattern completion. This could allow participants to report the appropriate item's orientation (Manohar *et al*., 2019). The bold line represents activation though pattern completion. **(C)** However, when participants are presented with a compound probe, such as used in many previous studies, the probe holds not only the colour cue, but also irrelevant information on an orientation that is different from the encoded item. This additional information could interfere with reactivating items from memory (dashed bold line). In this example, the probe's orientation might interfere with irrelevant information previously stored such as another orientation (flash).

If such probes do indeed interfere with retrieval, then many tasks which aim to measure memory capacity, such as the adjustment/reproduction paradigms, might actually systematically underestimate memory capacity (Bays & Husain, 2008; Zhang & Luck, 2008). Moreover, interference arises in many cognitive

domains including response selection, planning and dual-task processing (Schumacher et al., 2018). These cognitive functions are also underpinned by working memory (Shallice et al., 1996), and unimpeded recall of task-relevant information from WM may be a crucial component of executive function in general. Thus, interference effects observed at the time of WM recall could potentially shed light on interference effects in many other domains. In particular, interference at the time of a memory probe could also potentially explain interference in situations involving task rules. Storing and executing task rules may be homologous to working memory storage and recall respectively, and may involve similar pattern-completion mechanisms.

In the current study, we asked whether reducing the interaction between the probe and memory items – by removing the irrelevant feature from the probe – improves performance. We employed a new reporting method in which the probe contains only the relevant cue feature that indicates which memory item to recall – rather than combining the cue feature with an irrelevant feature – while still providing an analogue measure of memory precision. For example, if the task is to recall the direction of a coloured arrow, we initially show a central coloured dot as a probe, to indicate which item must be recalled, rather than a coloured orientated arrow that must be adjusted. To report the remembered arrow's direction, participants moved the mouse in the desired direction. Once the mouse moved, an arrow appeared pointing in that direction, so that the direction could subsequently be adjusted. We hypothesized that when their memory was interrogated with such a “bare” (dot) probe, participants would be able to give

more precise responses compared to the usual situation in which a coloured arrow is presented right from the start of the probe period.

One possible explanation for any interference identified at the time of probe could be that the probe arrow somehow "overwrites" perceptual information stored in a shorter term visual buffer such as iconic memory. If there were such iconic memory buffer (Kosslyn, 1980; Sperling, 1960)that supplements WM precision, the visual arrow probe might interfere with that perceptual store. Thus, in a second experiment we tried to erase any such buffer by a visual mask. So, if probe interference operates by disrupting iconic memory, then masking would be expected to reduce the degree to which the probe degrades performance.

Finally, according to the pattern-completion hypothesis, probe interference should arise when items must be re-activated from memory (Manohar et al., 2019). But several studies have demonstrated that one item in memory may be held in a privileged state, which may be more active than other stored items (Lewis-Peacock et al., 2012; Stokes et al., 2013; Wolff et al., 2017; Zokaei, Manohar, et al., 2014; Zokaei, Ning, et al., 2014). For example, the last item in a sequence is recalled more easily – the "recency effect" – perhaps because its memory remains in the active state (Gorgoraptis et al., 2011; Nee & Jonides, 2008, 2011, 2013; Öztekin et al., 2010; Zokaei et al., 2011). If reactivation were only required for earlier items in a sequence, a clear prediction is that interference from the probe should only affect the earlier items.

2.2 Materials and Methods

Participants

We tested 15 participants in Experiment 1 (4 male; M = 25.47; SD = 3.68; 1 left-handed); 15 individuals (10 male; M = 26.73 years; SD = 4.37; 0 left-handed) in Experiment 2; and another 15 participants (8 male; M = 25.8 years; SD = 3.28; 1 left-handed) took part in Experiment 3. All were neurologically normal and naive to the purpose of the experiment. The study was approved by the local ethics committee and participants gave their informed consent.

Experiment 1: Simultaneous Presentation

STIMULI

Stimuli were presented at a viewing distance of approximately 60 cm on a 24-inch LCD-monitor. Each memory array consisted of differently coloured arrows (approximately 2.5° × 0.4° of visual angle) that were chosen from 8 easily distinguishable colours (red, green, blue, yellow, cyan, violet, white, orange) presented on a black background, spaced along the boundary of an imaginary circle (radius 6.5°) around fixation with equal inter-item distances (center to center). All arrows within a single memory array were differently coloured, and were oriented in random directions (angles distributed uniformly over 360 degrees). Specifically, randomisation was achieved using Matlab's "rand"-function to sample values continuously and uniformly between 0 and 1 and then multiplying those by 2*π.

PROCEDURE

Each trial began with the presentation of a central fixation cross (white, approximately 1° diameter) for 500 milliseconds (ms), followed by a memory array (**Fig. 2.2A**). This memory array consisted of either three or five arrows displayed for a period of 1000 ms, followed by a black screen of 4000 ms. At the end of each sequence, recall for one of the items was tested. In the standard "arrow probe" condition, the probe constituted a randomly orientated arrow of the same colour as the target item, at the centre of the screen. Participants were instructed to rotate the probe using a computer mouse to match the remembered orientation of the item of the same colour. The mouse cursor began at the centre of the screen, and when the mouse was moved outside a circle radius of 0.7 degrees, the arrow orientation changed to point in the direction of the mouse movement (i.e,. the direction from the centre of screen to the mouse coordinate). In the novel "dot probe" condition, initially a dot of the target item's colour (1.3° diameter) was shown at the centre of the screen, instead of the arrow. Once the mouse was moved, this dot *changed into* the arrow probe, making it possible to point the arrow in the intended direction just as in the arrow-probe condition.

Each of the participants performed 4 practice trials consisting of the four different conditions presented in the experiment. For explanatory purposes these practice trials were significantly longer than the real trials. After this practice phase, participants performed 4 blocks of 124 trials each. Each block consisted of 31 trials for each of the four possible conditions mentioned above (2 probe type x 2

number of items presented). Trial types were present in equal numbers and their order was shuffled within each block.

Experiment 2: Mask condition

STIMULI

As in Experiment 1, the memory array consisted of three differently coloured arrows, positioned just as in the first Experiment's three-item condition.

PROCEDURE

Fixation period and memory array were identical to the first Experiment, followed either by a black screen or a "mask" of 1000 randomly oriented, randomly coloured and randomly positioned arrows, which were in both cases presented for 500 ms and followed by a black screen of 3500 ms (**Fig. 2.3A**). At the end of each sequence, recall for one of the items was tested as per Experiment 1, again the probe was either an arrow, or initially a dot of the target colour at the centre of the screen that changed to an arrow when the mouse is moved. As per Experiment 1, participants performed 4 practice trials for explanatory purposes. After this practice phase, participants performed 4 blocks of 124 trials each. Each block consisted of 31 trials for each of the four possible conditions mentioned above (2 probe type x 2 mask/no mask). The order of different possible trials was shuffled randomly within each block.

Experiment 3: Sequential Presentation

STIMULI

Stimuli were presented at a viewing distance and on a monitor as per Experiments 1 and 2. Each memory array consisted of four sequentially presented arrows of different colours (approximately 2.5° × 0.4° of visual angle) presented on a black background. The arrows appeared at random equally spaced locations on the boundary of an invisible circle (radius 6.5°) around fixation. Colours and orientations were chosen randomly as per Experiments 1 and 2.

PROCEDURE

A fixation period as per Experiments 1 was followed by a memory array. This memory array consisted of four sequentially shown arrows, displayed for a period of 500 ms each, and a black screen for a period of 500 ms after each, except for the last arrow which was followed by a 2500 ms black screen. At the end of the sequence, recall for one of the items was tested by displaying a probe as per Experiments 1 and 2 (**Fig. 2.4A**).

Each of the participants performed 8 practice trials consisting of the eight different conditions presented in the experiment. For explanatory purposes these practice trials were again significantly longer than the real trials. After this practice phase, participants performed 4 blocks of 72 trials each. Each block consisted of 9 trials for each of the eight possible conditions mentioned above (2 probe type x 4 target position in sequence). The order of different possible trials was random

throughout each block. Participants were able to decide whether they wanted to have a break and how long they wanted to pause after each block.

PRECISION CALCULATION

We defined the absolute error in recall as the unsigned difference in response angle from target angle. Response precision (the reciprocal of the circular SD of errors) is approximately proportional to the reciprocal of the absolute error. The mean absolute error was compared between conditions using 2-way repeated-measures ANOVA. All trials with subject's response times of 5 s and over were excluded for further analysis as these could be identified as outliers (mean + three times standard deviation, **Fig. S2.1**). Across all conditions, this criterion excluded an average of 1.22% (SD = 2.23%) of trials per subject in experiment 1, 0.93% per subject (SD = 1.38%) in experiment 2, and 3.96% (SD = 4.76%) per subject in experiment 3. We re-ran the analysis without this exclusion criterion for the main paradigms and were able to reproduce the results (**Supplementary Table 1**).

To model sources of error, we used a Bayesian hierarchical model of the mixture-of-von-Mises model (Bays et al., 2009) in R and JAGS as presented by (Oberauer et al., 2017)to estimate the relative contribution of precision, target-response, non-target response and guessing. Non-target responses are 'swap errors' in which participants report the orientation of one of the other, unprobed items in the memory array. Random-guessing responses are selected from a uniform distribution. For this purpose, 2500 adaptations, 5000 iterations and 4 chains were used.

2.3 Results

Experiment 1: Simultaneous Presentation

To test whether the mean absolute error was worsened by probe interference, a 2x2 ANOVA of probe type x set size was performed. There was an overall significant main effect of probe type, i.e., of whether the memory probe started off as an arrow, or was initially just a dot (Fig. 2.2B, $F(1,14) = 5.88$, $p = .029$, $\eta_p^2 = 0.296$). Thus, recall precision was significantly lower with an arrow probe. As expected there was also a main effect of number of items presented ($F(1,14) = 127.22$, $p < .001$, $\eta_p^2 = 0.901$). There was no interaction between set size and probe type ($F(1,14) = 0.58$, $p = .459$, $\eta_p^2 = 0.040$).

We compared models that allowed either setsize, probe type, both factors (and their potential interaction) or neither of these two factors to have an effect on the model parameters using the WAIC. For this purpose, priors were set to the same values over the four different models. The results support – similar to the ANOVA – a model of both factors without interaction. We plotted the sources of error and precision for the full interaction model (Fig. 2.5). In the above models, the probe type could influence both precision and probability of reporting the correct target item. In addition, we tested fits for models that allowed probe type and setsize to have an effect on guessing. In most cases, the WAIC preferred models that don't allow an effect on guessing. Next, we asked whether a probe type model that only allowed an effect on precision or target response was the best fitting model (Table

1). The comparison of WAICs showed that the precision model was the best fitting model.

We also investigated whether the type of probe influenced the time to begin moving the mouse, from the moment the probe was presented on the screen (Fig. S2.2). A 2x2-ANOVA of number of items x probe type showed that there was no significant difference in the time to initiate responses ($F(1,14) = 1.76$; $p = .21$; $\eta_p^2 = 0.112$), between arrow and dot conditions. As expected, their responding was slower for the 5-item condition ($F(1,14) = 14.54$; $p = .002$; $\eta_p^2 = 0.509$) but with no interaction ($F(1,14) = 0.05$; $p = .83$; $\eta_p^2 = 0.004$).

One further way in which the probe may drive errors is if the initial probe angle biases responses. To look for such an effect, we plotted the signed angular error, i.e. the difference between target and response angle, against the difference between initial probe angle and target angle (**Fig S2.3**). To do this, we examined only arrow-probe trials, collapsed across the other conditions in each experiment. The quantiles of the response error are shown as coloured lines, calculated in sliding window bins of width 20% over the possible relative probe orientations. Possible theoretical patterns of probe interference are (i) increased interference when probe is similar to the target, (ii) when probe is dissimilar to the target, (iii) tendency to report angle closer to probe, or (iv) tendency to report angle as further away from probe's orientation (**Fig S2.3A**). But rather than following any of these patterns, interference from the probe appeared to be independent of the probe's orientation (Fig S2.3B).

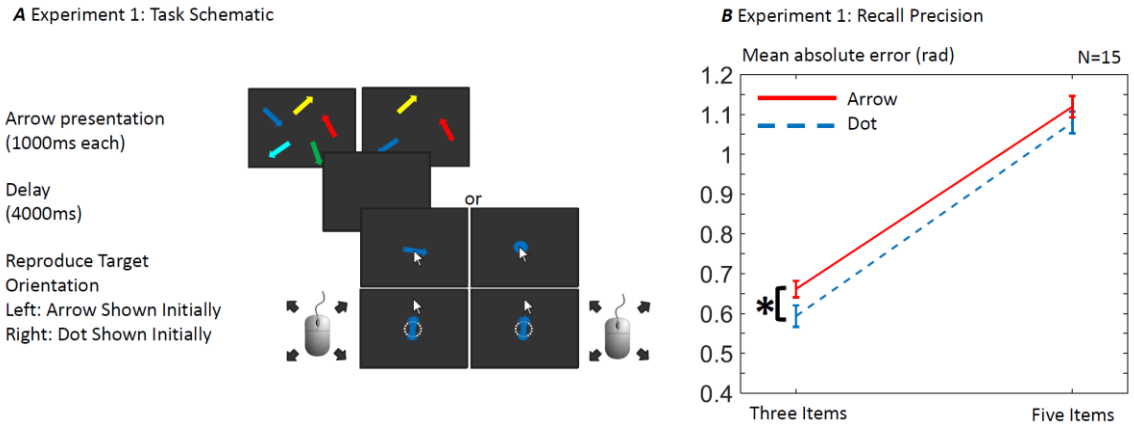


Figure 2.2 | Design and mean absolute error for Experiment 1. (A) Participants had to remember the orientations of a set of coloured arrows. Three or five items were presented in the memory array, and after a delay, one of the arrows was probed by their colour. In the 'arrow probe' condition, the probe was a compound object, that is, a coloured arrow that had to be adjusted to the remembered orientation, by moving the mouse. In the 'dot probe' condition, the probe was a coloured dot (no irrelevant orientation information, colour only), which turned into an arrow as soon as the mouse was moved. **(B)** The arrow probe significantly impaired recall–precision (p = .029). As expected, memory was worse when more items had to be stored (p < .001), but there was a significant interaction between the probe type and number of items in the array. The error bars were calculated by subtracting each subject's grand mean away from their individual per-condition values and showing ± the standard error (Loftus & Masson, 1994).

Experiment 2: Masking

For the second experiment, we performed a 2x2 ANOVA of probe type x mask on mean absolute error. The results of experiment 1 were replicated, with a significant main effect of probe type ($F(1,14) = 14.66$, $p = .002$; $\eta_p^2 = 0.511$). The presence of the mask significantly increased error (main effect of mask vs. no-mask, $F(1,14) = 16.51$, $p = .001$; $\eta_p^2 = 0.541$) suggesting that the mask effectively erased some visual information, making it significantly more difficult for participants to reproduce the arrow correctly. However, the mask did not abolish the effect of probe type, indicated by no interaction between probe type and masking ($F(1,14) = 0.98$; $p = .338$; $\eta_p^2 = 0.066$). Specifically, recall was worse for the arrow probe than the dot-probe ($t(14) = 2.66$, $p = .019$, **Fig. 2.3B**).

We performed the same hierarchical Bayesian models as in experiment 1, comparing model fits if either probe type, masking, both (and their potential interaction) or none of the factors were allowed to have an effect on the modelling. The comparison of WAIC again - similar to the results of the ANOVA – prefer a model of both effects, probe type and masking (**Table 2**). In most cases, the WAIC preferred models that don't allow an effect on guessing. And again, we plotted the soures of error and precision for the full interaction model (**Fig. 2.5**). A subanalysis of a probe type model that allowed either an effect on precision or target response showed a preference for the model that allowed an effect on precision.

As in experiment 1, there was no difference in the time to begin ($F(1,14) = 0.77$; $p = .39$; $\eta_p^2 = 0.052$) responses between arrow and dot conditions, nor mask vs. no-

mask conditions ($F(1,14) = 0.90$; $p = 0.36$; $\eta_p^2 = 0.052$), nor was there an interaction ($F(1,14) = 1.46$; $p = .25$; $\eta_p^2 = 0.095$).

Again, there was no indication that the initial probe angle biased responses (**Fig S2.3C**).

In order to provide better power to detect effects of probe type on sources of error, we pooled data across experiments 1 and 2. The combined analysis indicates that the probe interference has effects on guessing as well as target-responses and precision (**Supplementary Table 9**).

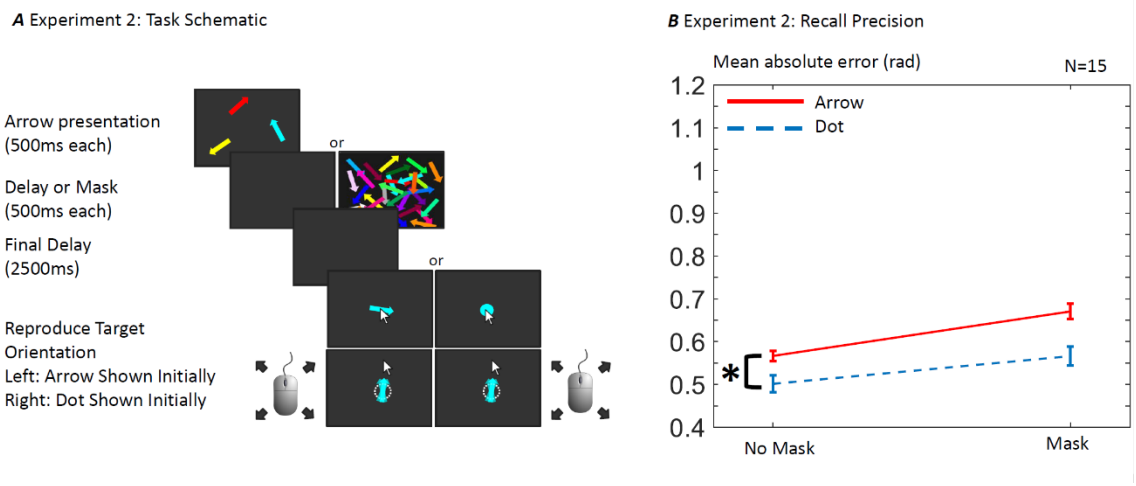


Figure 2.3 | Design and mean absolute error for Experiment 2. (A) Three arrows were presented in the memory array and either followed by a mask of 1,000 randomly orientated and coloured arrows or a black delay screen. The probe could be a coloured arrow or dot, just as in Experiment 1. **(B)** Replicating the interference effect observed in Experiment 1, we found that recall was worse with a compound probe ($p = .003$). Masking also significantly impaired recall–precision ($p = .002$). But crucially, there was no interaction between the probe type and masking. The error bars were calculated by subtracting each subject's grand mean away from their individual per-condition values and showing ± the standard error (Loftus & Masson, 1994).

Experiment 3: Sequential Presentation

For the mean absolute error, we performed a 2 x 4 ANOVA of probe type x serial position. This showed a significant interaction between probe type and position of the target item in the sequence ($F(3,42) = 3.83$; $p = .016$; $\eta_p^2 = 0.215$). As expected, there was also a main effect of the position of the target item in the sequence ($F(3,42) = 21.83$, $p < .001$; $\eta_p^2 = 0.609$) but not of probe type ($F(3,42) = 3.44$, $p = .085$; $\eta_p^2 = 0.197$). Pairwise t-tests demonstrated that recall error in the arrow probe was only higher in the second ($t(14) = 2.205$, p = .045) and third ($t(14) = 3.383$, $p = .004$) but not in the first (t(14) = 0.963, p = .352) and last serial positions ($t(14) = 1.195$, $p = .252$; **Fig 2.4B**). Yet, when only the second through fourth items were included in the analysis, the interaction did not show to be significant ($F(2,26) = 0.77$, $p = .473$; $\eta_p^2 = 0.056$).

The lack of effect for the first item could not be explained by performance being at chance, i.e. a floor effect (Kolmogorov-Smirnov test for responses to first item vs chance, $p < 0.001$ for both arrow- and dot-probe) (**Fig S4**).

As per experiments 1 and 2, we used the comparison between the different hierarchical model fits allowing probe type, sequence position, both of them (and their interaction) and none of those to have an effect on the model parameters. The WAIC preferred a model including only an effect of sequential position, closely followed by the “both effects” and “interaction” models (Table 3). In most cases, the WAIC preferred models that don’t allow any effects on guessing. Sources of

error and precision are plotted separately for the full interaction models (Fig. 2.5). According to our proposed pattern-completion hypothesis, responses should take longer for items at positions one to three (which must be retrieved) compared to the last item (which is in the focus of attention). Using an ANOVA, there was no main effect of probe type ($F(1,42) = 0.021$; $p = .886$; $\eta_p^2 = 0.002$) or sequence position ($F(3,42) = 2.11$; $p = .113$; $\eta_p^2 = 0.131$) on the time to begin responses. There was also no interaction of these two ($F(3,42) = 2.722$; $p = .056$; $\eta_p^2 = 0.163$).

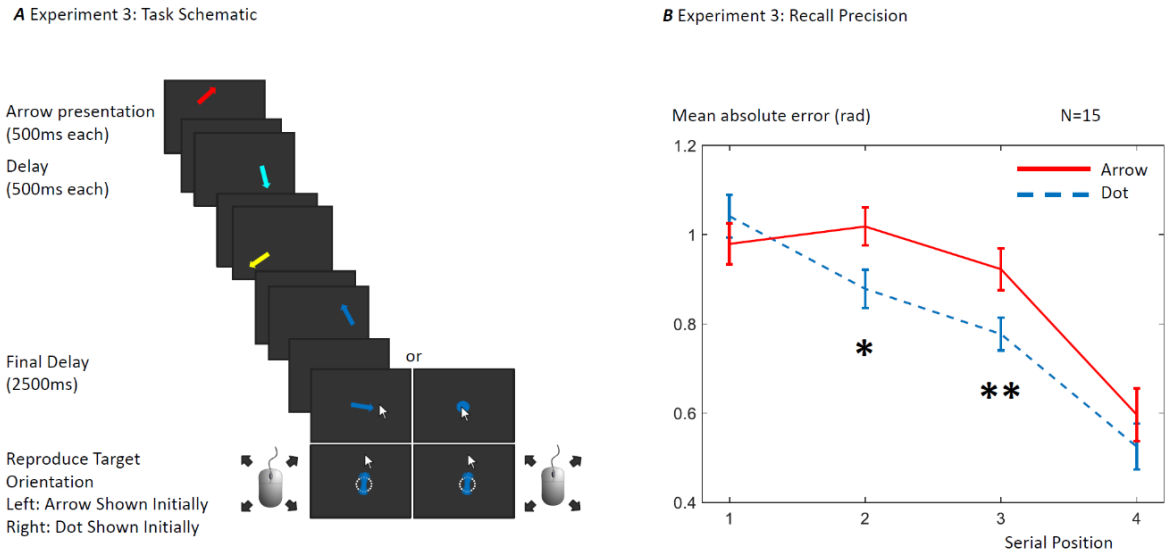


Figure 2.4 | Design and mean absolute error for Experiment 3. (A) Four coloured arrows were sequentially presented in the memory array. The probe could be a coloured arrow or dot, as previously described. **(B)** There was a significant interaction between the probe type and the serial position of the target item in the sequence ($F(3,39) = 5.19$, $p = .004$). Pairwise tests indicated that recall error was greater for the arrow probe only for the second ($p = .016$) and third ($p = .004$) serial positions, but not for the first ($p = .26$) or last item ($p = .31$) in the sequence. The error bars were calculated by subtracting each subject's grand mean away from their individual per-condition values and showing ± the standard error (Loftus & Masson, 1994).

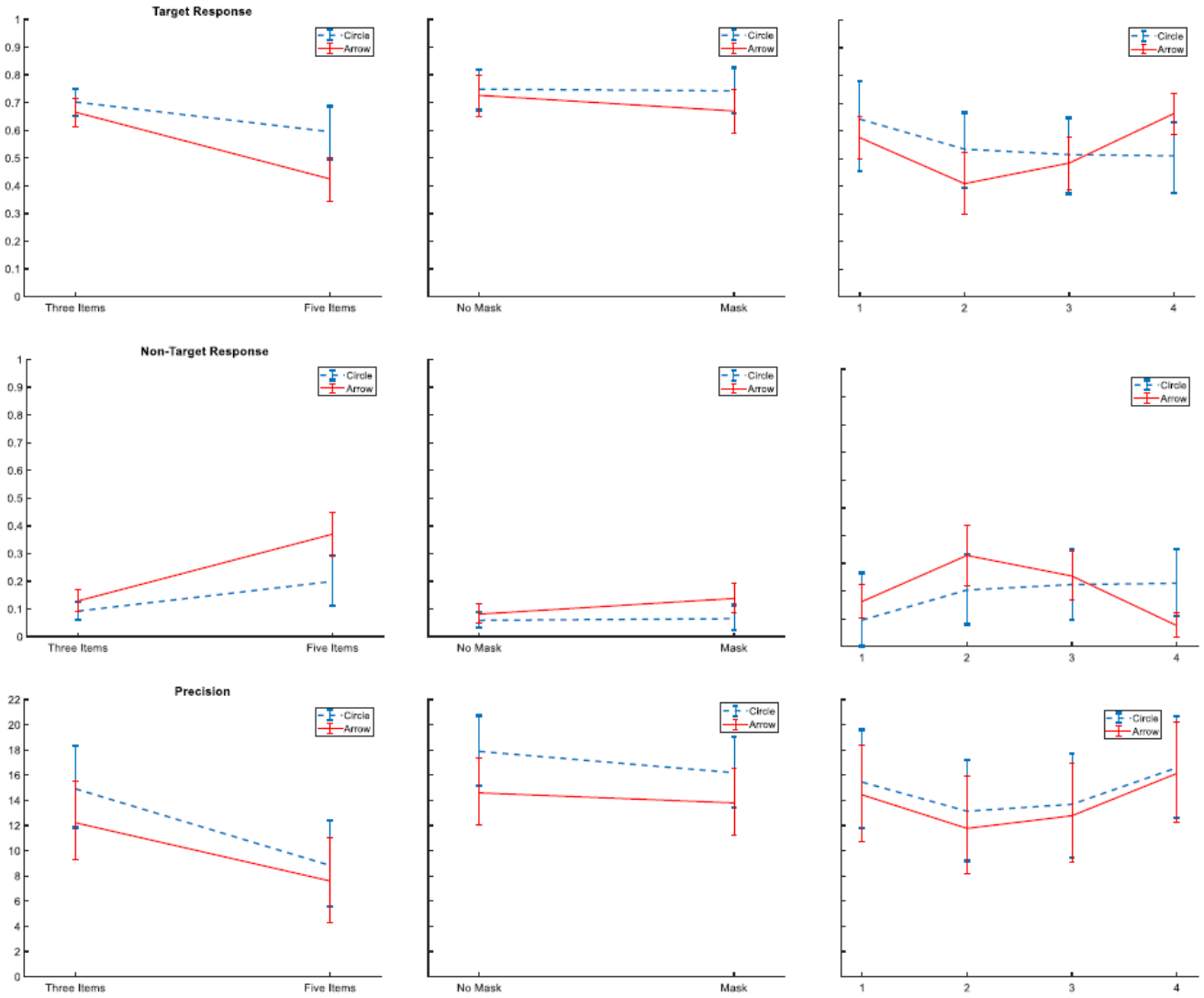


Figure 2.5 | Plots of Bayesian hierarchical model fits for Experiments 1–3 (left to right). Plots for target response in the first line, for non-target responses in the second line, for guessing responses in the third line, and for precision in the bottom line. Error bars represent highest density interval from a sample of representative values, estimated as shortest credible interval (Oberauer et al., 2017).

2.4 Discussion

The experiments reported here aimed to test whether irrelevant features presented as part of the memory probe, at the time of retrieval, are detrimental to recall. We compared performance in the case where the probe initially contained a feature on the dimension that had to be recalled (coloured arrow probe), with a case where there was initially no information on the feature dimension to be recalled (coloured dot probe). The results of our first experiment showed that the presence of this feature significantly impaired participants' precision, as they performed significantly better when the probe was initially a colour-only dot (**Fig. 2.2B, Fig. 2.3B, Fig. 2.4B**).

Many methods of measuring WM involve presenting a probe that contains a feature on the dimension to be recalled, that is not the correct feature value to be recalled. For example, adjustment tasks involve a probe that already holds an orientation which may or may not match the target. The method of adjustment allows measurement of the precision of recall, but may corrupt retrieval of the recalled object by interference from the probe. This impairment could be significantly decreased by using a colour-only probe, in which the probe is initially just a coloured dot. Importantly the probe type did not influence the reaction time to begin the motor response, indicating that even though retrieval was improved with the colour-only probe, it cannot be accounted for by a longer response time – e.g. a speed-accuracy trade-off or less impulsive responding. In addition, there

was no context effect that would reduce the observed results to a benefit or deficit due to probe type switches between trials.

In Experiment 2, we asked whether the observed effects arise because the irrelevant feature in the probe overwrites perceptual information. If there were a visual immediate buffer that holds additional information about the most recently presented visual information, such as an iconic store, interference from the additional probe feature might overwrite the additional immediate buffer. Although both probe interference and the addition of a mask significantly reduced precision of recall, there was no interaction, suggesting that the degree of interference by the probe was not attenuated by the introduction of a mask. Assuming that the mask disrupted any purely perceptual, iconic buffer, then the arrow probe must degrade performance by a different mechanism.

According to some models of WM, probes trigger retrieval by re-activating the features of corresponding items in memory (Farrell & Stephan, 2002; Sandberg et al., 2003). One item in memory may already be in the focus of attention, which means that its features are already active, in a response-ready state. Items that are not currently in the focus of attention at the time of recall must first be re-activated by the probe, in order to generate a response. One example of an attentional focus may be the recency effect, in which the last item in a sequence is recalled better, perhaps because its features are held in an active state (Blalock & Clegg, 2010; Gorgoraptis et al., 2011; Hay et al., 2007; Zokaei et al., 2011). In this case, interference from the irrelevant probe features would be expected to impede recall only when the item must be re-activated from a non-focused state,

i.e., for non-final items. Therefore, we conducted the third experiment in which we presented a set of four items in a sequence to participants.

The results showed that the last item was immune to disruption by the arrow. However, the second and third items were not. This suggests that the presence of a compound probe selectively disrupts the focusing of earlier items in the sequence. Items that were recalled better due to recency effect however were not influenced by probe interference. Thus, we saw a significant interaction of probe type and position of the target item in the sequence. Yet, this interaction did not hold when only the second to fourth items were included in the analysis. Also, recency did not show a reaction time benefit. These somewhat ambiguous results could point at the fact that the last item in the sequence might have been in the focus of attention but is not anymore at the time of probing. Or, it might be in the focus of attention in some trials while it isn't in others. The fact that there is no reaction time advantage for the last item further suggests that the last item might not (anymore) be in the focus of attention. This idea will be further expanded on in the General Discussion. Several authors have considered whether this most recent item might automatically be held in the focus of attention. An associative pattern completion model predicts worse recall accuracy for unfocused items, when an irrelevant feature on the dimension to be recalled is present in the probe (Manohar et al., 2019). This is because they have to be brought into the focus of attention by re-activation, and this process is subject to interference. In the next

empirical chapter, it will be further explored whether the effect can be reproduced in recency and also in retro-cueing.

However, it does not explain why the first item in the sequence is also immune to the effect. Primacy effects in visuospatial WM tend to be small and their mechanism is poorly understood, but may involve association between the first item and the preceding context, as proposed for episodic memories, perhaps relying on the medial temporal lobe. An alternative explanation of probe interference in general could be that the inner items in a sequence are at least partly held in a different kind of store, for example in episodic memory, which is harder to retrieve from (Öztekin et al., 2009, 2010). It is however difficult to determine if long-term memory is involved in the case of the first item. The lack of probe interference for the first item in the sequence is unlikely to be a floor effect, because performance for the first item is still better than chance (Fig.S2.4).

When sources of error in the Bayesian hierarchical approach for the mixture model were estimated, model comparison indicated an independent main effect of interference in the first and second experiments (Table 2.1&2.2). The computational modelling permitted us to distinguish between possible mechanisms of interference, in addition to simply quantifying the errors caused by interference. Estimates of the sources of error (Fig. 2.5) suggest that the arrow probe both increased misbinding to non-target stimuli, and decreased response precision, independently of masking, and amplified by larger set size.

In the third experiment, the interference is manifest in reduced precision (Table 3), with (Fig. 2.5) misbinding being reduced especially in the second sequential position.

According to the pattern-completion hypothesis, we expected that responses in the last experiment should take longer for items at positions one to three (which must be retrieved) compared to the last item (which is in the focus of attention). Our data did not, however, support this (Fig. S2.2). Without interference, the time to initiate responses is relatively independent of serial position, but the probe interference may selectively slow retrieval for 'middle' items in the sequence. Possible reasons for the lack of effect could be that the task permits adjustment, so participants may move the mouse before completing retrieval. Another possibility is that probe interference increases retrieval error without slowing the process of pattern completion itself – this possibility is supported by the increase of misbinding errors, which in the model would comprise erroneous completions of a valid memory item. It is also possible that our sample size might not be adequately powered to reveal small changes in reaction time. Therefore, further studies would help confirm the presence of the model-predicted reaction time effects.

Our task required participants to simply move the mouse in the direction of the remembered arrow. Comparing with other tasks, it is important to distinguish carefully between tasks in which a decision must be made based on the probe stimulus, and tasks which require simply reporting items in memory. If information

at the time of probe must interact with corresponding information in the memory item, for example in change detection, comparisons with memory, or in recall-by-adjustment paradigms, then we should consider those tasks as involving more than just memory recall. They additionally involve a decision process, and interference at recall may manifest in the decision-making components of these tasks. Comparing these more complex paradigms to simple report, with and without interference, may enable separation of these recall and decision-making components (Myers et al., 2017).

Task sets themselves are likely to involve WM, especially in complex tasks (e.g. Schumacher et al., 2018)). Conflict between task rules (eg as seen in the Simon task) might thus involve similar mechanisms to those involved in WM retrieval. In particular, task rules can be viewed as an associative mapping between stimulus and response – in the same way as WM binding between features of an object. On this view, selecting a response in response conflict tasks involves matching a cue to the appropriate rule in memory. Response selection in response to a cue can be considered as a motor analogue of recalling a memory item in response to a probe. Conversely, working memory can be regarded as a "ready-state" for selecting and re-activating recently encountered information (Myers et al., 2017). Specifically, if choosing an appropriate action after a cue involves a kind of pattern-completion, it should be subject to the interference effects similar to probe effects studied here. Indeed response conflict correlates with WM capacity (Duncan et al., 2008), with costs arising from interference between task representations, rather than simply from additional stimuli or responses (Schumacher et al. 2018). This supports the idea that task representations themselves are cognitively costly and

may at least partly tax WM. Such an equivalence between the processes of executing task rules and recalling items in WM would generate a range of testable predictions for future studies.

Our results, consistent with the conclusions of Souza, Rerko & Oberauer (2016), demonstrate that the method of probing can itself impact on WM precision, and this interference is likely to be relevant to many previous studies that use well-established probing methods. The pattern of interference is consistent with a pattern-completion account of recall. The recency effect provides resilience to this interference, as predicted by accounts of the focus of attention. These findings are in keeping with an account in which visual WM representations are content addressable, associative, and modulated by attention, with interference playing a crucial role in forgetting.

In conclusion, our findings suggest that the probe in WM experiments can interfere with recall, and the process of retrieval is modulated by a number of factors including the focus of attention.

Table 1.1. | WAIC values of Hierarchical Bayesian measurement mixture models for experiment 1

	Effects allowed on Target-Response and Precision	Effects allowed on Target-Response, Guessing Response and Precision
No effect	13618.380	13607.520
Probe effect only	13543.921	13549.762
Setsize effect only	13283.385	13393.291
Both effects	13248.453*	13370.171
Both effects and interaction	13250.460	13353.313*
Probe effect only, On Precision only	13550.639†	13543.791†
Probe effect only, On Target Response only	13565.585	13552.556

* Best model fit main analysis,
† best model fit sub-analysis

Table 1.2 | WAIC values of Hierarchical Bayesian measurement mixture models for experiment 2

	Effects allowed on Target-Response and Precision	Effects allowed on Target-Response, Guessing Response and Precision
No effects	7910.483	7905.507
Probe effect only	7851.580	7850.399*
Mask effect only	7856.709	7863.681
Both effects	7838.427*	7853.540
Both effects and interaction	7843.414	7850.881
Probe effect only, On Precision only	7842.153†	7851.524†
Probe effect only, On Target Response only	7863.517	7868.239

* Best model fit main analysis, † best model fit sub-analysis

Table 1.3 | WAIC values of Hierarchical Bayesian measurement models for experiment 3

	Effects allowed on Target-Response and Precision	Effects allowed on Target-Response, Guessing Response and Precision
No effect	7487.645	7488.79
Probe effect only	7432.999	7426.596
Sequence effect only	7331.279	7386.903
Both effects	7339.379	7386.408*
Both effects and interaction	7326.635*	7405.406
Probe effect only, On Precision only	7437.266	7425.68†
Probe effect only, On Target Response only	7435.024†	7426.272

* Best model fit main analysis, † best model fit sub-analysis

2.5 Supplementary Materials

Merged datasets confirm strong probe-type effects for all sources of error

In addition to the analysis presented above, we pooled trials from the "three items, dot vs. arrow"-condition of Experiment 1 and of the "no mask, dot vs. arrow"-condition of Experiment 2. Taking absolute error of this combined dataset, we performed a repeated measures ANOVA with repeated measures on probe type and the between-subject factor "group". Results showed a strongly significant main effect of probe type ($F(1,28) = 15.55$, $p < 0.001$, $\eta_p^2 = 0.357$), but no interaction of group and probe type ($F(1,28) = 0.007$, $p = 0.934$, $\eta_p^2 = 0.000$). Concerning between-subjects effects, there was also no significant main effect of group ($F(1,28) = 1.38$, $p = 0.251$, $\eta_p^2 = 0.047$).

We also merged the same conditions for the pilot data (three items dot vs. arrow and no mask, dot vs arrow) to perform a repeated measures ANOVA on absolute error. Again, there was a strongly significant main effect of probe type ($F(1,29) = 13.33$, $p = 0.001$, $\eta_p^2 = 0.307$), but no interaction of group and probe type ($F(1,29) = 1.121$, $p = 0.298$, $\eta_p^2 = 0.026$). Concerning between-subjects effects, there was also no significant main effect of group ($F(1,29) = 0.35$, $p = 0.558$, $\eta_p^2 = 0.012$).

These analyses further support the case of the arrow probe impairing working memory precision, with the probe type effect presenting with a significantly high effect size in both cases.

Supplementary Graphs

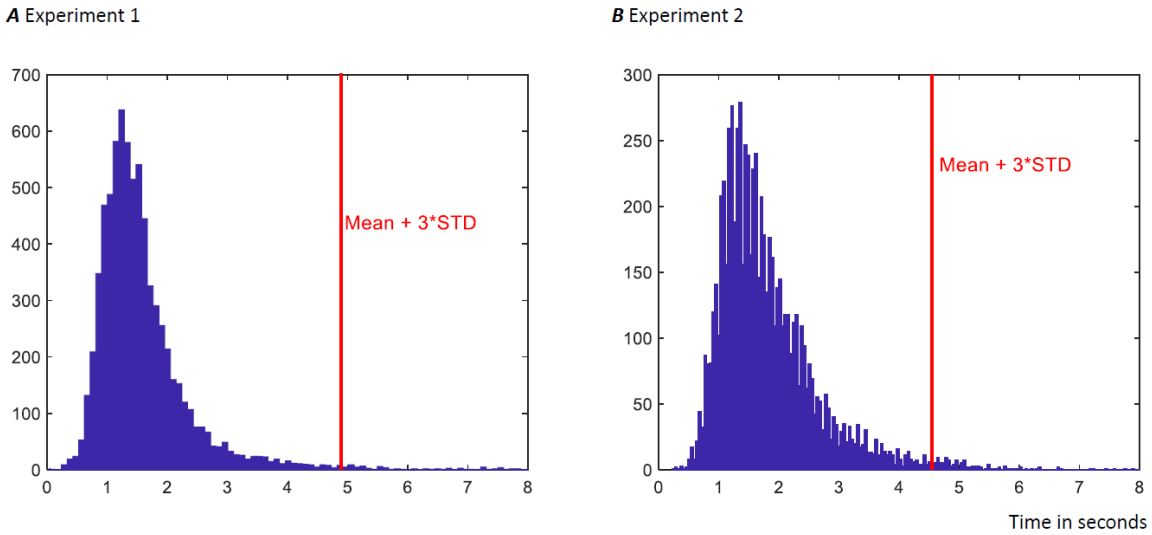


Figure S2.1 | Histograms of the period from moment the probe appears in the screen to finishing the response in experiment 1 (A) and 2 (B). Trials in which participants took more than five seconds to respond were excluded from further analysis as they were longer than the mean reaction time plus three times the standard deviation (red vertical line).

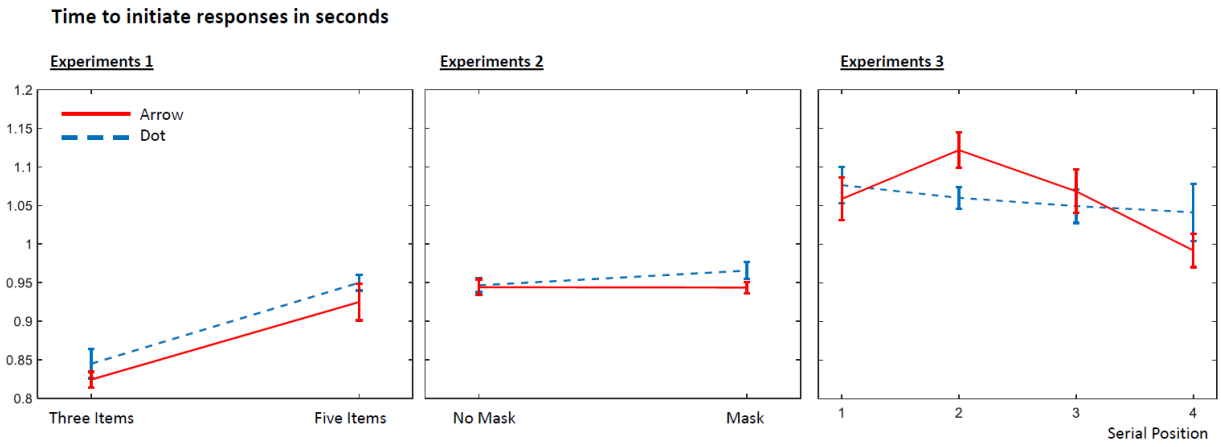


Figure S2.2 | Times to initiate responses from the moment, the probe appears on the screen. The left panel shows times for the simultaneous presentation of 3 or 5 arrows, the middle panel times for the Masking experiment, and the right panel times for the sequential presentation of stimuli. Red lines indicate the arrow probe, blue lines indicate the dot probe. The error bars were calculated by subtracting each subject's grand mean away from their individual per-condition values, and showing +/- the standard error (Loftus & Masson, 1994).

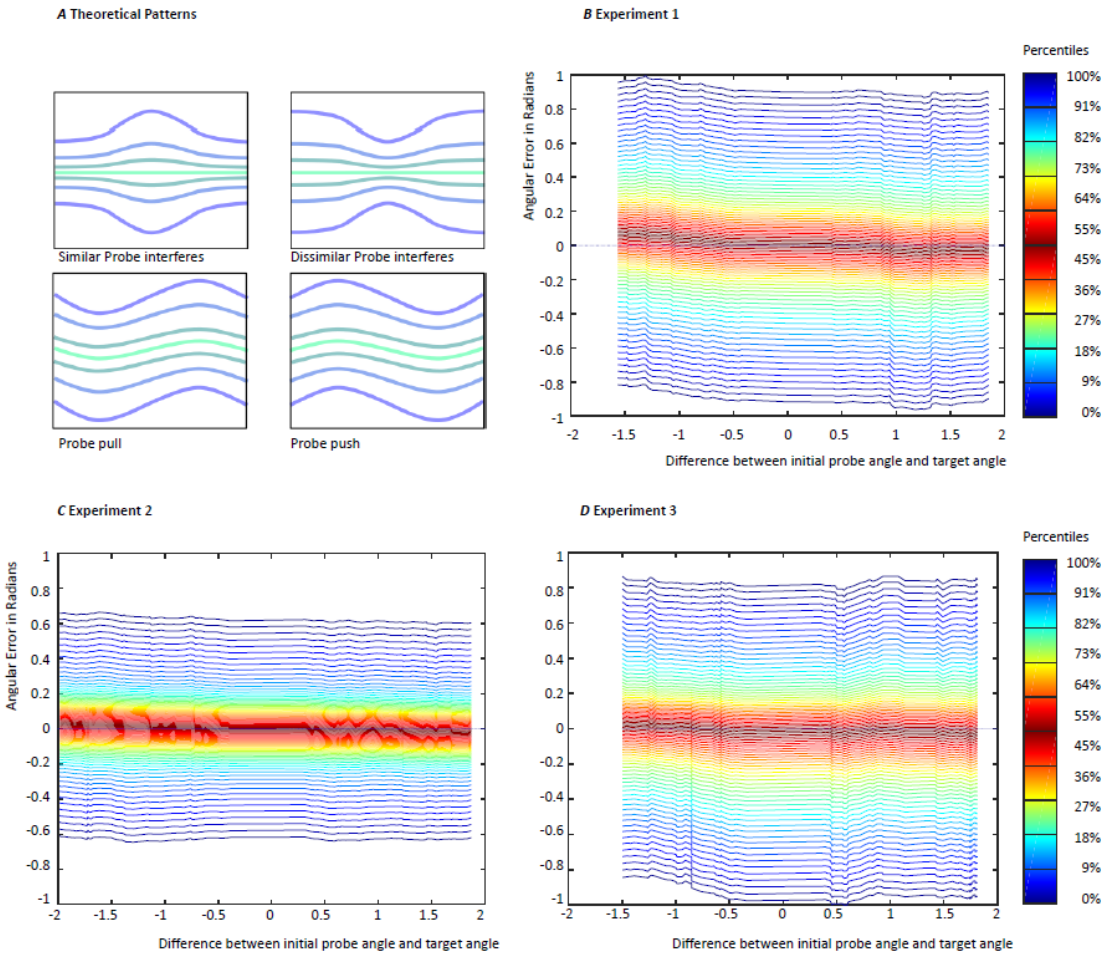


Figure S2.3 | Angular error, the difference between target and response angle, against the difference between initial probe angle and target angle. We compared the results of our three experiment with theoretical pattern of interference of probes that (i) are similar to the target, (ii) of probes that are dissimilar to the target, (iii) of probe pull, when responses are likely to be pulled to the probe's orientation and (iv) of probe push, when responses are likely to be pushed away from the probe's orientation (A). There were no similarities for experiments 1 (B), 2 (C) or 3 (D).

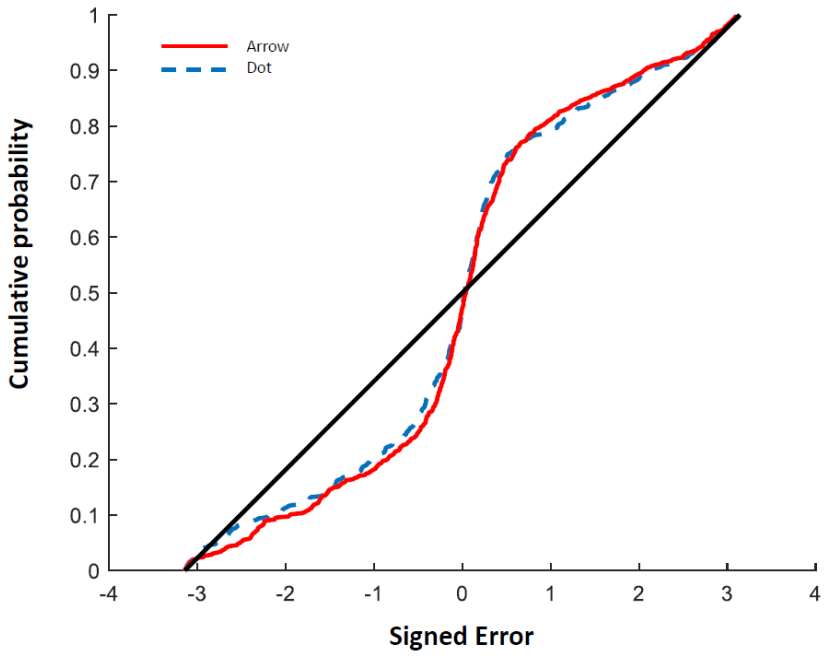


Figure S2.4 | Empirical distribution function of signed error in responses for the first sequentially presented item in experiment 3. The red solid line represents trials in which the first presented item was an arrow and the blue dashed line represents trials in which the first sequentially presented item was a dot. The black solid diagonal line represents the chance distribution expected with no information about the target. Independent of the probe type, responses for both items were significantly different from a guessing response ($p < 0.001$).

3. Recency but not retro-cued shifts of attention protects working memory from interference

The previous chapter showed privileged items to be protected from interference caused by the probe itself. Those items were prioritized because they were presented last within a sequence. The following chapter will show how this is not the only way of prioritizing items but that another way of moving items into the focus of attention, namely retro-cueing, needs further investigation in order to conclude whether information in the focus of attention is protected no matter the way it was moved there in the first place.

3.1 Abstract

Working memory allows us to keep multiple pieces of information in mind, ready for use. Some items are prioritised, in a more readily accessible form than others, and are considered to be in the "focus of attention". A key unanswered question is what determines whether an item is prioritised. At least two distinct factors are relevant. First, the last item in a sequence may naturally occupy the focus of attention, simply due to its *recency*. Second, making a previously encoded item task-relevant can elevate it into the focus of attention, through retrospective *cueing*.

Here, across four experiments, we demonstrate that these two routes to attentional prioritisation deploy dissociable mechanisms. We used a visual working memory task in which participants remember a set of objects and, at

recall, the test probe contained features that interfere with retrieval. Recency protected items against probe interference, whereas retrospective cues did not, despite speeding up retrieval. When two sequential retrospective cues were used, they had additive effects, rather than acting as a movable focus of attention. Finally, when recency was pitted directly against retrospective cueing, the results revealed that these two prioritisation mechanisms operate in parallel.

Recency benefits might arise not because the last item in the sequence remains active, but rather, because its latent representation is not overwritten by subsequent items encoded into WM. Recency and retro-cueing might differentially engage active versus synaptic mechanisms of memory.

3.2 Introduction

To cope with the hustles and bustles of daily life, we constantly need to change what we focus on at any moment. For example, when attending to an interesting talk, you might also check on the equally interesting reactions to your last twitter post on your phone. This ability requires a flexible resource that allows you to rapidly prioritize one piece of information over the other, without forgetting other information still in mind. Remembering and manipulating multiple objects over short delays constitutes the primary role of working memory (LaRocque et al., 2014). Prioritizing certain items within WM over others is the hallmark of flexible cognition. A prioritised item in WM is considered to be in the "focus of attention"

(Olivers et al., 2011; Zokaei, Manohar, et al., 2014; Zokaei, Ning, et al., 2014). An item in the focus of attention is recalled faster and with more precision, potentially because it is in a response-ready state (Lewis-Peacock et al., 2012; Stokes et al., 2013; Wolff et al., 2017; Zokaei et al., 2011; Zokaei, Manohar, et al., 2014). The focus of attention also seems to provide protection against interference which is an important cause of forgetting (Oberauer & Lin, 2017; Souza & Oberauer, 2016). Interference is driven by several factors: by other items held in working, and by the amount of time the information is stored in memory (Pertzov et al., 2017), by interfering information that has to be ignored (Fallon et al., 2017; Hu et al., 2014) and by the information present at the time of recall itself (Souza et al., 2016; Tabi et al., 2019).

An item within WM could become prioritized in WM in at least two ways. On the one hand, when items are encoded into WM sequentially, the last item in a sequence might automatically remain in an active state (Niklaus et al., 2019). This might explain the *recency effect*, where the last item in a sequence is retrieved more accurately than preceding items (McElree, 2006; McElree & Dosher, 1989) and explain why adding new irrelevant visual information after the last item attenuates this benefit (Hu et al., 2014). On the other hand, attention can be directed towards information during the delay, long after memoranda have been encoded into WM (Lepsien & Nobre, 2007). Using a retrospective cue or *"retro-cue",* attention can be directed selectively to enhance the representation of an item in WM which, as a result, is recalled faster and more accurately (for a review: Souza & Oberauer, 2016; Souza & Oberauer, 2016; van Moorselaar et al., 2015). Importantly, a retro-cue does not provide participants with any additional

information about the memoranda. Rather, the benefit must arise because the item assumes a special status within WM (i.e. Astle et al., 2012; Zokaei et al., 2014). In fact, numerous studies have shown that a remembered item relies on different neural representations when inside and outside the focus of attention (LaRocque et al., 2014 for a review on state-based models in short-term memory).

The similarities in benefits from retro-cueing and recency could suggest that they both rely on a *common protection mechanism*, conferred by the focus of attention to mitigate against any effect of interference that might corrupt recall of an item. If that were the case, an item that is presented last in the sequence (recency) should not benefit further from being retro-cued, as it is already in the focus of attention. However, in a set of three carefully designed experiments, Niklaus et al. (2019) provided evidence against this hypothesis. They measured the time course of retrieval in a short-term recognition task and found that a retro-cue benefitted the final item in the sequence equally as much as the preceding items. There was no interaction of recency and retro-cueing, suggesting that the effects are in fact additive and thus independent. But this study crucially did not directly test whether the two benefits protected items against interference.

Here we investigate this issue by examining interference at retrieval. Prior research has shown that retrieval is impaired when irrelevant features are present in the test probe. For example, if participants are asked to remember the colours and orientations of a series of arrows, a recall probe with the same colour as an encoded arrow, but with a random orientation, impairs recall compared to a

simple colour cue (Tabi et al. 2019; **Fig. 3.1A**). Curiously, in that study, probing the last item in the sequence in this manner did *not* show interference from the probe, suggesting that recency provided protection. Retro-cues, in contrast, slightly weaken interference at the time of probe but do not abolish it (Makovski et al., 2010), indicating that even if an item is supposedly in the focus of attention, it is still susceptible to probe interference. However, the latter study induced interference in a different way, comparing choices between a target and a non-target option against simple change detection.

Interference caused by recall cues is predicted by models of WM in which retrieval works through pattern completion (Manohar et al., 2019; Rolls, 2013), a mechanism that allows the retrieval of a whole object when cued by only one of its features. This is the case in a recent model developed by Manohar and colleagues (2019), in which rapid synaptic plasticity creates a stable attractor for each item encoded into memory. In this model, features of an object are bound together as a pattern of strengthened synapses between individual feature units and a single conjunction unit **(Fig. 3.1B)**. This framework allows one item in memory to be neurally active, where the conjunctive unit and associated features sustain each other's activity. The last-accessed item in memory is held in the active state, while the others remain as "activity-silent" synaptic traces. Subsequently presenting a single, previously encoded feature can reactivate the corresponding object's conjunction unit, which in turn re-activates the rest of the associated features. Thus, accessing or cueing an inactive item in memory can bring it into a prioritised, active state, akin to the *focus of attention*.

A key consequence of the pattern completion mechanism is that retrieval can be blocked if unrelated features are presented as a part of the retrieval cue. For example, a probe containing a *random* orientation in addition to a colour may potentially block the re-activation of the *associated* orientation, just as found empirically (Tabi et al. 2019).

This neural model provides two possible explanations for why the last item in a sequence is robust to interference as also shown previously (Tabi et al. 2019). The first account builds on the fact that the last-encoded item is already in an *active state* at the time of recall, and so it does not require pattern completion in order to be active. This makes it resistant to the distortion caused by the irrelevant probe features. The second explanation invokes *synaptic overwriting*. When new items are encoded, they carve out a new attractor state in the synaptic weights, and the synaptic traces of previously encoded items may be partly overwritten, making them harder to re-activate.

In the present study, we aimed to examine which of these two mechanisms is responsible for the resistance against probe interference. We hypothesized that if the protection from probe interference relies solely on the item being in the focus of attention at the time of recall, retro-cuing it before recall should protect it against interference. But if instead the robustness to probe interference relies solely on synaptic strength, elevating an item into the focus of attention before presentation of the probe should *not* provide any additional protection if it had previously been unattended. The results show that although retro-cueing and

recency both improve participants' performance, only recency protected items from probe interference. Even though retro-cues are capable of shifting the focus of attention and improving performance, they cannot reverse the effect of overwriting caused by the encoding of other items. Only the most recently encoded item carries the benefit of not being overwritten, which provides it with a crucial protection against probe interference.

3.3 General Methods

Participants

Twenty individuals that met the age criterion (18-35 years) were recruited for each of the four experiments. All participants were naïve to the purpose of the experiment, reported to be neurologically normal and had normal or corrected to normal vision. Our study was approved by the local ethics committee. All participants gave their informed consent and were financially reimbursed for their time.

Stimuli

Stimuli were presented on a 24-inch LCD-monitor with a viewing distance of approximately 60 cm. Memory arrays consisted of a series of oriented coloured arrows (**Fig. 3.1A**). Colours were picked from eight easily distinguishable colours (red, green, blue, yellow, cyan, violet, white and orange) and no colour in the memory array appeared twice in one trial. The stimuli (approximately 2.5° × 0.4° of visual angle) were presented on a black background and drawn on an imaginary circle with radius of 6.5° of visual angle from the centre marked with a fixation cross. In Experiment 1, the three stimulus locations were equally spaced around this circle, with a random angular offset on each trial, whereas in Experiments 2-4, the two stimuli were presented on a horizontal through the centre of the screen. The arrows' orientations were drawn independently from a uniform distribution.

Recall precision

Absolute error in recall was defined as the unsigned difference between the response and the target angles. Response precision, defined as the reciprocal of the circular SD of errors, is approximately proportional to the reciprocal of absolute error. Statistical comparisons of absolute error were performed using either 2- or 3-way repeated measures ANOVA (2x3 in Experiment 1, 2x2 in Experiments 2 and 4, 2x2x3-ANOVA in Experiment 3).

3.4 Experiment 1: Probe Interference for Sequential items

The goal of the first experiment was to show that recency provides *protection against probe interference* for the last item of a three-item sequence.

Method

Procedure

In Experiment 1, three arrows were presented sequentially for a period of 500ms each followed by a blank screen of 500ms after each arrow (**Fig. 3.1A**). After a final black screen of 2500ms following the final arrow, participants were presented with either a randomly oriented arrow, or a dot, in the colour of one of the items in the memory array the orientation of which they had to reproduce. The task was a three-item version of the four-item sequential task reported in Tabi et al. (2019). At test, the mouse cursor appeared in the centre of the screen. Participants were instructed to adjust the probe's orientation using the computer mouse to match the remembered item's orientation. When the mouse cursor was moved outside a circle with a radius of 0.7° of visual angle, the arrow's orientation changed to point in the direction of the mouse movement, so that the arrow pointed from the screen centre towards the current mouse cursor coordinate.

In half of the trials, i.e., the "dot probe" condition, the probe started as a central dot and changed into an arrow once the mouse was moved outside the 0.7° radius.

In the other half of the trials, i.e., the "arrow probe" conditions, the probe started as a randomly oriented arrow. Participants confirmed their choice with a mouse click that triggered the start of a new trial. Each item in the sequence was equally likely to be tested. The experiment contained six different experimental conditions (first/second/third item probed & dot/arrow probe) split into four blocks of 78 trials. Each block consisted of 13 trials per condition that were randomly shuffled within a block.

In this and all experiments reported here, participants were first shown on-screen instructions, and then performed one trial of each condition with the opportunity to repeat this training until they confirmed that they understood the task's instructions. Participants were allowed a break between blocks to avoid fatigue, the length of which they could determine themselves. The whole experimental session lasted on average 1 hour.

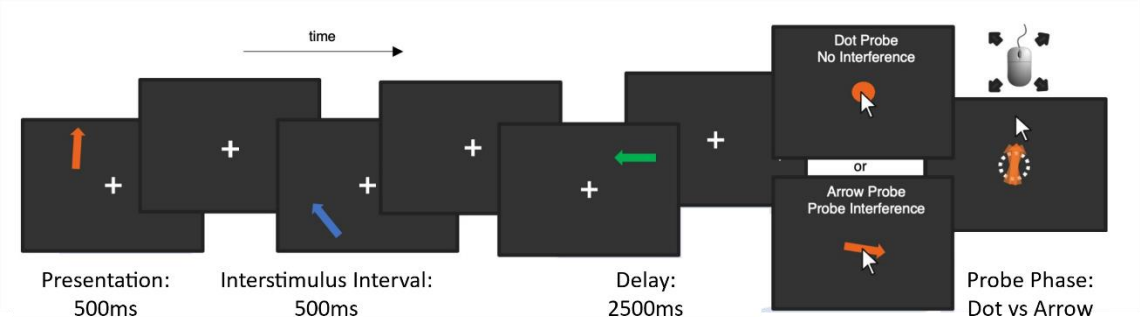


Figure 3.1 | An example trial sequence from Experiment 1 including two types of test probe: no interference probe (dot probe; top) and interference probe (arrow probe; bottom). Participants were asked to remember the orientations of three arrows presented sequentially over a delay period and, at test, reported the orientation of one of them. The arrow probe, unlike the dot probe, included a feature from the to-be-recalled dimension, i.e., orientation, causing interference during recall of the remembered orientation.

Results

The goal of the first study was to assess the amount of probe interference as a function of items' sequential position.

Absolute error

A 2x3 ANOVA of probe type x sequential position was performed on the mean absolute error. As expected, recall precision was significantly higher with later items in the sequence (Fig. 3.2, main effect of sequential position F (2,38) = 27.28, p < 0.001, η_p^2 = 0.589), and significantly worse when participants started with an arrow probe than with a dot (main effect of probe type type F (1,19) = 42.63, p < 0.001, η_p^2= 0.692). Notably, there was an interaction between sequential position and probe type (F(2,38) = 4.16, p = 0.023, η_p^2 = 0.180).

Post-hoc t-tests conducted for the differences between the dot and arrow condition in each of the three sequential positions, show that the interference is greatest for the first (t(19) = 5.12, p < 0.001), intermediate for the second (t(19) = 2.86, p = 0.010) and weakest for the last item of the sequence (t(19) = 2.37, p = 0.029). These results are in line with previous findings for four sequential items (Tabi et al. 2019).

Reaction time

To understand why the last item did not suffer from interference, we examined the time taken to recall the orientation. We investigated whether sequential

position or probe type had an effect on the time to initiate response (**Supplementary Fig. 3.1A**). A 2x3-ANOVA of probe type x sequential position revealed no significant difference in the time to initiate responses between dot and arrow probe ($F(1,19)$ = 2.284e-4; p = 0.988; η_p^2 = 0.000). Later items were, however, recalled faster ($F(2,38)$ = 5.11; p = 0.011; η_p^2= 0.212) with an interaction between the two factors ($F(2,38)$ = 4.28; p = 0.021; η_p^2= 0.184).

The time cost of interference was numerically smallest for the final item (**Supplementary Fig. 3.1A**).

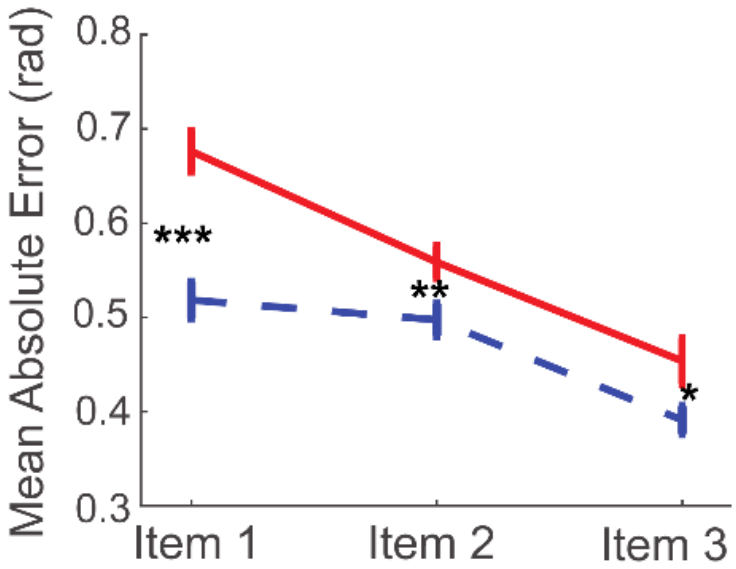


Figure 3.2 | Mean absolute error for Experiment 1. Absolute error showed a main effect of sequential position and probe type (indicated by the asterisk). There was a significant interaction between sequential position and probe type showing less probe interference for the most recent item compared to earlier items. Error bars were calculated by subtracting each subject's grand mean away from their individual per-condition values and showing +/- the standard error (Loftus & Masson, 1994

Discussion

In Experiment 1, we successfully reproduced previous behavioural findings showing that the most recent item of a sequence is more protected against probe interference compared to their earlier counterparts (Tabi et al., 2019).

We reasoned that *if* the protection is endowed by an item in WM being in the active state, then re-activating an item during the delay should also protect it against interference. So, next, we examined what happens when an item held in WM is retro-cued during the delay which, according to current conceptual frameworks, should elevate it into the focus of attention.

3.5 Experiment 2: Probe interference after a single Incidental Retro-cue

The goal of the second experiment was to test whether simply paying attention to an item during the delay also protects this item against probe interference. To shift attention to one item in memory, after encoding, participants were shown a word denoting a colour of one of the two arrows they were holding in memory (**Fig. 3.3A**). They were asked simply to indicate the remembered spatial *location* of the corresponding item during encoding, with a left or right mouse click. Thus, this item became temporarily relevant to the task, entering a prioritized state. Because the location is irrelevant to the final orientation report task, this task has been termed "incidental retro-cueing" and has been shown to improve recall when the cued item is the same as the finally probed item (Zokaei et al., 2011). If this kind of prioritisation provides protection against probe interference, we hypothesized that the cued item should no longer show a behavioural decrement in the arrow condition.

Method

Procedure

In Experiment 2, two arrows were presented simultaneously for a period of 500ms (**Fig. 3.3A**). After 500ms of blank screen, participants were presented with the name of the colour of one of these two items in the centre of the screen. The letters were also coloured in that particular colour. Participants had to report whether the item of the indicated colour was previously presented on the left or

right half of the screen by clicking the left or right mouse button accordingly. Participants' response was followed by a delay of 2500ms. As in Experiment 1, at test participants were either presented with a randomly oriented coloured arrow, or a coloured dot.

The item probed by the retro-cue and at test was either the same (½ trials valid retro-cue) or different (½ trials invalid retro-cue), and the test probe was either an arrow (½ trials) or a dot (½ trials) probe. This generated four different conditions (valid/invalid retro-cue & dot/arrow probe) split into four blocks of 100 trials each. Each block consisted of 25 trials per condition that were randomly shuffled within a block.

Results

The purpose of Experiment 2 was to test whether attention protects against probe interference, comparable to the protection conferred to the last item of a sequence observed in Experiment 1.

Absolute error

For the analysis of this experiment, we excluded trials in which participants did not respond correctly in the incidental retro-cue task, i.e., when they were probed for the left item but clicked right. On average, 1.55% (SD = 1.43) of trials per participant were excluded according to this criterion. A 2x2-ANOVA of retro-

cueing x probe type showed that especially the retro-cue effect was the most prominent effect (**Fig. 3.3B**, main effect of retro-cueing, F (1,19) = 31.58, p < 0.001, η_p^2 = 0.624). This indicates better recall when the retro-cued item was identical to the item probed for in the orientation task, in line with previously observed benefits of valid retro-cues (Zokaei et al., 2014). Recall was worsened by probe interference in the regular ANOVA (main effect of probe type, F(1,19) = 5.94, p = 0.025, η_p^2 = 0.238), i.e. when the memory probe started off as an arrow, compared to when it was initially just a coloured dot, in line with experiment 1. Notably, there was no interaction between retro-cueing and probe type (F(1,19) = 1.62, p = 0.218, η_p^2 = 0.079), suggesting that probe interference was not reduced for the validly cued item.

Reaction time

We also tested whether retro-cueing or probe type had an effect on the time to begin moving the mouse in order to make a response, from the moment the probe appeared on the screen (**Fig. S3.1B**). A 2x2-ANOVA of retro-cueing x probe type revealed no significant difference in the time to initiate responses between dot and arrow probe (F(1,19) = 0.74; p = 0.400; η_p^2 = 0.038). Participants were faster to initiate responses with a valid vs. invalid retro-cue (F(1,19) = 17.80; p < 0.001; η_p^2 = 0.484) but with no interaction between the two factors (F(1,19) = 1.26; p = 0.276; η_p^2= 0.062).

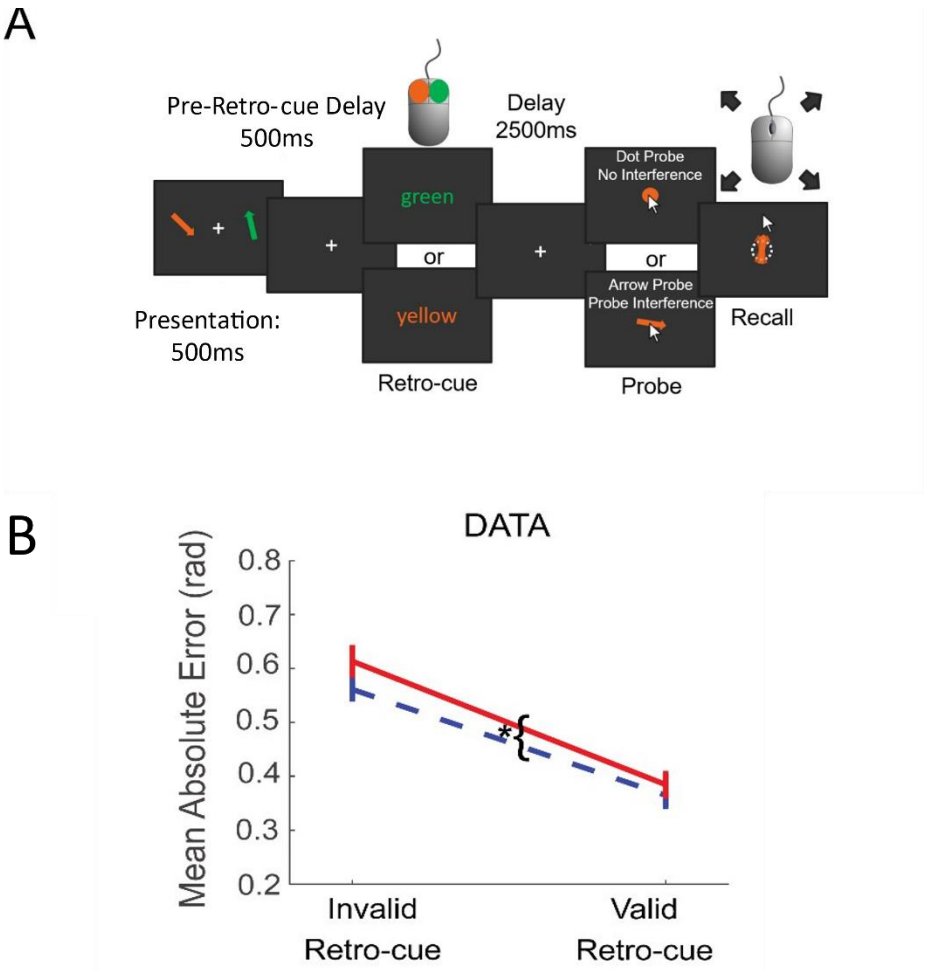


Figure 3.3. Design and mean absolute error for Experiment 2. (A) Participants were asked to remember the orientations of two arrows. After a delay, an incidental retro-cue was used to ask participants to report the side on which one of the two items was presented. Following a delay, participants were asked to report either the orientation of the retro-cued (valid retro-cue condition) or the other item (invalid retro-cue condition). The test probe was either a coloured dot (no probe interference) or a randomly oriented coloured arrow (probe interference)**. (B)** Absolute error showed a main effect of retro-cueing and probe type (indicated by the asterisk) but no interaction. Error bars were calculated by subtracting each subject's grand mean away from their individual per-condition values and showing the standard error (Loftus & Masson, 1994) **(B, right)** In the model simulations, validly retro-cued items are recalled better, as expected. In contrast to empirical results, valid retro-cues protected against probe interference.

Discussion

The results of Experiment 2 did not support our hypothesis that bringing items into an active state by focusing attention on them protects against probe interference. Even though validly cued items were recalled better, they were not protected from interference at the time of the probe (**Fig. 3.3**), unlike the last-presented item in Experiment 1. This finding is in line with some previous results from (Makovski et al., 2010) which demonstrated that probe interference was still present even if a retro-cue was used to move the target into the focus of attention.

Why would an interfering probe drive errors even when the correct item is already in the focus of attention?

The irrelevant probe feature *itself might act as an invalid retro-cue*. Therefore, it disrupts retrieval independent of the current focus of attention. The irrelevant probe feature can shift attention away from the correct item, and has additive effects to the preceding retro-cue. If this is indeed the case, then we might expect that *sequential* retro-cues would also have additive effects, that are independent of one another, i.e. the order of cueing should not matter.

3.6 Experiment 3: Sequential Retro-cues

Experiment 3 tested whether sequential retro-cues do indeed have independent effects. One might intuitively think that if a cue shifts attention to an item, then this would cancel out the effect of any previous cues. However, the main factors of experiment 2 indicated that the retro-cues and interference had independent effects on recall, suggesting that multiple retro-cues might also act independently of one another. To this end, we used *double retro-cueing* (Zokaei, Ning, Manohar, Feredoes & Husain, 2014) in which participants are presented with two items simultaneously, followed by a first and second retro-cue, each of which was 'incidental' as described above. On half the trials, both retro-cues were identical, and on the other half, different. When the retro-cues were different to each other, either the first or the second retro-cue was valid. We asked whether the last retro-cue dominates, or whether the two retro-cues would instead have independent, additive effects.

Methods

Procedure

As in Experiment 2, participants were presented with two arrows simultaneously (**Fig. 3.4A**). After a blank screen delay of 500ms, participants performed the same retro-cue task as in Experiment 2 (valid/invalid retro-cue condition). After another delay of 500ms, they were again presented with a retro-cue task of the same kind.

A final delay of 3000ms preceded the test probe. In this experiment, participants were only presented with a dot probe. There was thus no probe-interference condition. In half of the trials, the first retro-cue was valid and in half of the trials the cue validity was repeated (valid, valid/ invalid, invalid) generating 4 different conditions (first retro-cue valid vs. invalid x both retro-cues same vs. different). In total, participants performed 320 trials (80 trials per condition) divided into four blocks.

Results

Absolute error

Trials in which participants failed in one or both incidental retro-cue tasks were excluded from further analysis (M = 2.42%, SD = 1.89) per participant. A 2x2 ANOVA of first retro-cue valid vs. invalid x same vs. different retro-cues was performed to test whether, similar to a sequential effect, participants performed better when the second vs. the first retro-cue was valid. This ANOVA showed an overall significant main effect of the first retro-cue's validity, i.e. whether the first retro-cue was valid or not (**Fig. 3.4B**, $F(1,19) = 5.35$, $p = 0.032$, $\eta_p^2 = 0.220$). There was no effect of whether the item in the first and second retro-cue task was identical vs different ($F(1,19) = 0.00$, $p = 0.953$, $\eta_p^2 = 0.000$). There was a close-to significant interaction of these two factors ($F(1,19) = 4.03$, $p = 0.059$, $\eta_p^2 = 0.175$).

To test whether the last retro-cue had stronger effects than the first, we performed post-hoc t-tests. In particular, we examined trials where the retro-cues

were different and tested whether performance was better when the item that was cued by the second retro-cue was probed, compared to when the item cued first was probed. There was no significant difference in performance as function of valid cue order, i.e., whether the first or second retro-cue was valid ($t(19) = 0.06$, $p = 0.950$; blue line in **Fig. 3.4B**). However, as expected, when both retro-cues were the same, participants performed significantly worse in the double invalid retro-cue condition compared to the double valid retro-cue condition ($t(19) = -2.53$, $p = 0.020$; red line in **Fig. 3.4B**).

Reaction time

We investigated whether the validity of the first retro-cue (valid vs. invalid) or the similarity between the validity of the first and second retro-cue had an effect on the response initiation times (**Supplementary Fig. 3.1D**). A 2x2 ANOVA revealed no significant difference in the time to initiate responses for a valid vs invalid first retro-cue ($F(1,19) = 3.99$; $p = 0.060$; $\eta_p^2 = 0.174$). There was also no significant effect of whether both retro-cues were same or different ($F(1,19) = 4.25$, $p = 0.053$, $\eta_p^2 = 0.183$). There was, however, a significant interaction between these two factors ($F(1,19) = 10.83$; $p = 0.004$; $\eta_p^2 = 0.363$), indicating speed benefits specifically when both retro-cues were valid.

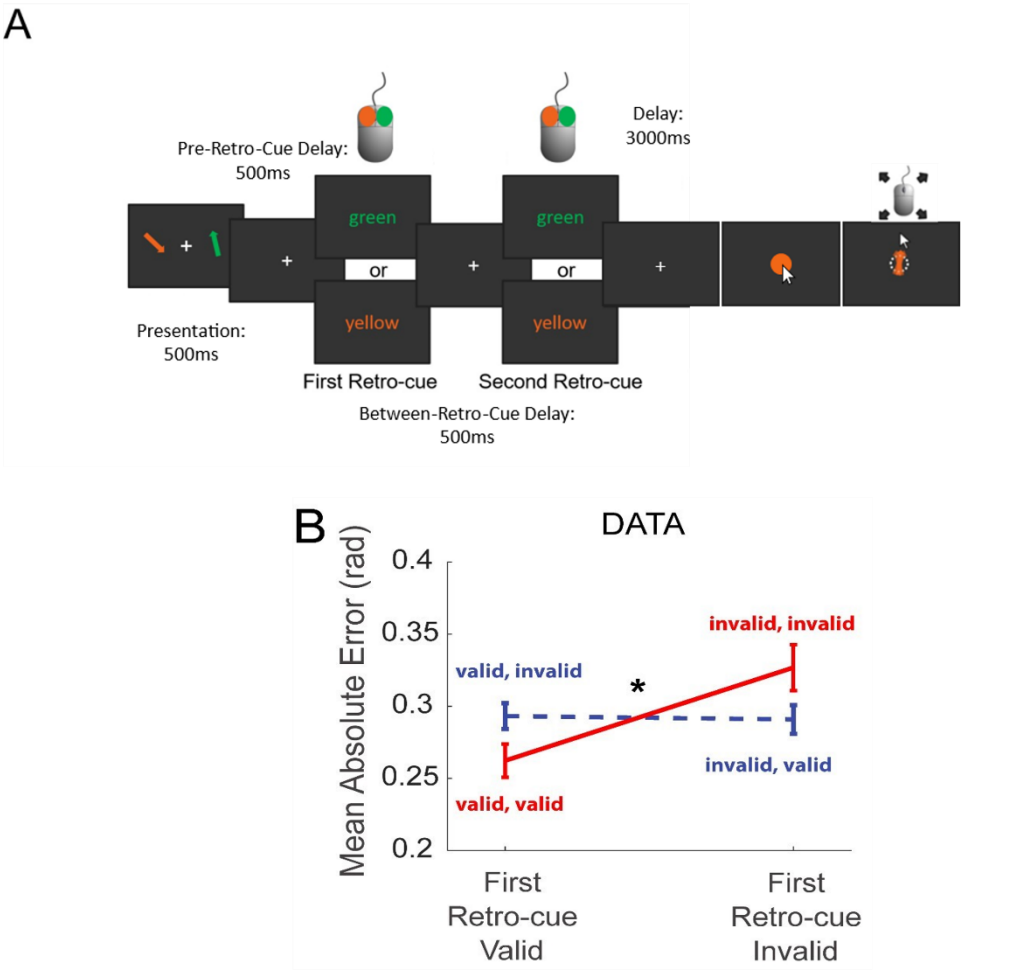


Figure 3.4 | Design and mean absolute error for Experiment 3. (A) Participants were asked to remember the orientations of two arrows. After a delay, an incidental retro-cue was used to ask participants to report the side on which one of the two items was presented. Following another delay, participants were asked to perform the same task again. In half of the trials, the second retro-cue was the same as the first one. The test probe was consisted of a coloured dot only (no probe interference manipulation). **(B)** Post-hoc T-test results for absolute error show that there is no sequential effect when retro-cues are different (blue dashed line) but as expected, there is a main effect of retro-cue validity (red solid line, significance indicated by asterisk). Error bars were calculated by subtracting each subject's grand mean away from their individual per-condition values and showing the standard error (Loftus & Masson, 1994).

Discussion

Experiment 3 tested whether serial retro-cues either have additive effects, or the last cue dominates over prior cues. We found additive effects only, with no dominance of the last-cued item. When two different items were sequentially cued within one experimental trial, the order in which this happens does not matter (**Fig. 3.4**). Another way to view this is that serial retro-cues do *not* generate a recency effect.

The results corroborate the idea that the recency effect produced at encoding seems to be qualitatively special, and according to the model could indicate a lack of retroactive interference from subsequently encoded items. If this is the case, a strong prediction is that retro-cues would benefit recall of *all* items in a sequence, but would not protect against interference. To test this, we directly compared recency and retro-cues in a single design.

3.7 Experiment 4: Probe interference in Retro-cued vs. Recency Benefits

In the fourth experiment, we ask whether the last item's protection against interference could be modulated by a retro-cue. For this purpose, we combined the sequential presentation of items (from Experiment 1) with subsequent valid or invalid retro-cue (from Experiment 2). If there were a single mechanism for the focus of attention, governed by both recency and retro-cueing, the retro-cue should transfer any benefits to the cued item. If, instead, recent items are protected by virtue of being encoded better, the retro-cue should *not* protect against interference.

Method

Procedure

As in Experiment 2, participants were presented with two arrows. However, the stimulus presentation was sequential with each arrow being presented for a period of 300ms with an inter-stimulus-interval of 1000ms (**Fig. 3.5A**). After a 500ms delay, participants either had to perform the same retro-cue task as in Experiment 2 (1/3 of trials valid condition and 1/3 of trials invalid retro-cue condition) or were shown a blank screen for another 500ms (1/3 of trials neutral condition). A final delay of 2500ms preceded the orientation task that, as in Experiments 1 and 2, presented participants with a dot probe in half of the trials or an arrow probe in the other half. In half of the trials, participants were probed for the first item. Overall, there were 12 different conditions (2 sequential

positions x 3 different retro-cue conditions x 2 probe types). In total, participants performed 384 trials (32 trials per condition) divided into four blocks.

Results

The goal of Experiment 4 was to test whether the increased resistance to probe interference observed for the last item in Experiment 1 could be shifted to an earlier item by a retro-cue.

Absolute error

Again, we excluded trials in which participants failed the incidental retro-cue task (M = 0.82%, SD = 0.90%). For this experiment, a 2x2x3 ANOVA of sequential position x probe type x retro-cueing on mean absolute error demonstrated that recall precision was significantly better with a valid retro-cue (main effect of retro-cueing, **Fig. 3.5B**, $F(1,19) = 4.12$, $p = 0.024$, $\eta_p^2 = 0.178$). Precision was also higher for the last item in the sequence (main effect of sequential position, $F(1,19) = 12.39$, $p = 0.002$, $\eta_p^2 = 0.395$). In addition, probe interference generally worsened performance (main effect of probe type, $F(1,19) = 10.91$, $p = 0.004$, $\eta_p^2 = 0.365$). Importantly, there was a significant interaction of sequential position and probe type, with interference occurring for the first but not last item of the sequence ($F(1,19) = 13.32$, $p = 0.002$, $\eta_p^2 = 0.395$), in line with the results of Expt 1. There was neither a significant interaction of retro-cueing and sequential position ($F(1,19) = 2.45$, $p = 0.100$, $\eta_p^2 = 0.114$) nor retro-cueing and probe type ($F(1,19) = 0.24$, $p = 0.787$, $\eta_p^2 = 0.013$), demonstrating equally strong interference whether an item

was retro-cued or not, in line with Expt 2. There was no three-way interaction ($F(1,19) = 0.83$, $p = 0.445$, $\eta_p^2 = 0.042$).

In a post-hoc analysis, we conducted individual 2x2-ANOVAs for the absolute error in: (1) conditions in which the retro-cue was invalid, (2) conditions, in which the retro-cue was valid and (3) neutral conditions in which participants were not required to perform a retro-cue task. For the invalid retro-cueing conditions, there was a main effect of sequential position ($F(1,19) = 7.38$, $p = 0.014$, $\eta_p^2 = 0.280$) as well as probe type ($F(1,19) = 6.03$, $p = 0.024$, $\eta_p^2 = 0.241$) and an interaction of these two ($F(1,19) = 4.88$, $p = 0.040$, $\eta_p^2 = 0.204$). Post-hoc T-Tests showed that the arrow probe increased absolute error compared to the dot probe in the first ($t(19) = -3.11$, $p = 0.006$), but not in the last item ($t(19) = -0.186$, $p = 0.855$), in keeping with protection by recency. In the valid retro-cue conditions, the ANOVA showed a main effect of sequential position ($F(1,19) = 6.54$, $p = 0.019$, $\eta_p^2 = 0.256$) and of probe type ($F(1,19) = 4.51$, $p = 0.047$, $\eta_p^2 = 0.192$). The interaction of these two factors ($F(1,19) = 4.32$, $p = 0.051$, $\eta_p^2 = 0.185$) showed a trend in the ANOVA. Post-hoc t-tests again demonstrated interference from the arrow probe in the first ($t(19) = -3.09$, $p = 0.006$) but not in the last item of the sequence ($t(19) = -0.654$, $p = 0.521$). For the neutral condition, the ANOVA showed a significant main effect of sequential position ($F(1,19) = 8.60$, $p = 0.009$, $\eta_p^2 = 0.312$) and an interaction of probe type and sequential position ($F(1,19) = 5.59$, $p = 0.029$, $\eta_p^2 = 0.227$) without a main effect of probe type in the ANOVA ($F(1,19) = 3.309$, $p = 0.085$, $\eta_p^2 = 0.148$). Again, T-tests showed no probe interference in the last ($t(19) = 0.30$, $p = 0.765$) but in the first item ($t(19) = 2.54$, $p = 0.020$). To summarize, the last of the two

items was protected from interference from the arrow probe, irrespective of whether that item had been brought into the focus of attention by a retro-cue.

Reaction time

We investigated whether retro-cueing, sequential position or probe type had an effect on the time participants took to initiate their response (**Supplementary Fig. 1C**). The 2x2x3-ANOVA revealed neither a significant difference in the time to initiate responses between dot and arrow probe ($F(1,19) = 0.51$; $p = 0.486$; $\eta_p^2 = 0.216$) nor the sequential position ($F(1,19) = 2.45$; $p = 0.134$; $\eta_p^2 = 0.114$). There was, however, a significant difference in initiation time for when participants started with a valid vs. invalid vs. no retro-cue ($F(1,19) = 5.23$; $p = 0.010$; $\eta_p^2 = 0.216$). In addition, there was a significant three-way interaction of the three factors in the ANOVA ($F(1,19) = 5.47$; $p = 0.008$; $\eta_p^2 = 0.223$). None of the three two-way interactions, retro-cueing*sequential position ($F(1,19) = 2.03$; $p = 0.145$; $\eta_p^2 = 0.097$), retro-cueing*probe type ($F(1,19) = 0.16$; $p = 0.854$; $\eta_p^2 = 0.008$) and sequential position*probe type ($F(1,19) = 1.73$; $p = 0.204$; $\eta_p^2 = 0.083$), were significant.

Following up on the significant three-way interaction in the regular ANOVA, we conducted three post-hoc 2x2-repeated-measures-ANOVAs (sequential position x probe type) for the three different retro-cueing conditions (i**nvalid**

Supplementary Fig. 1C left, valid Supplementary Fig. 1C middle, neutral Supplementary Fig. 1C right):

The 2x2-ANOVA of probe type and sequential position for the invalid retro-cueing conditions showed no significant main effect of sequential position (F(1,19) = 0.944, p = 0.343, η_p^2 = 0.047) or probe type (F(1,19) = 0.795, p = 0.384, η_p^2 = 0.040), nor an interaction of these two (F(1,19) = 0.206, p = 0.655, η_p^2 = 0.011). In conditions with a valid retro-cue, a 2x2-ANOVA of probe type and sequential position again showed no main effect of sequential position (F(1,19) = 1.74, p = 0.203, η_p^2 = 0.084) and probe type (F(1,19) = 0.07, p = 0.788, η_p^2 = 0.004), nor an interaction of these two (F(1,19) = 1.59, p = 0.223, η_p^2 = 0.077). The 2x2-ANOVA of probe type and sequential position in the neutral conditions showed no main effect of the sequential position (F(1,19) = 3.18, p = 0.091, η_p^2 = 0.143) or probe type (F(1,19) = 0.23, p = 0.64, η_p^2 = 0.012). But there was a significant interaction of these two (F(1,19) = 8.31, p = 0.01, η_p^2 = 0.304).

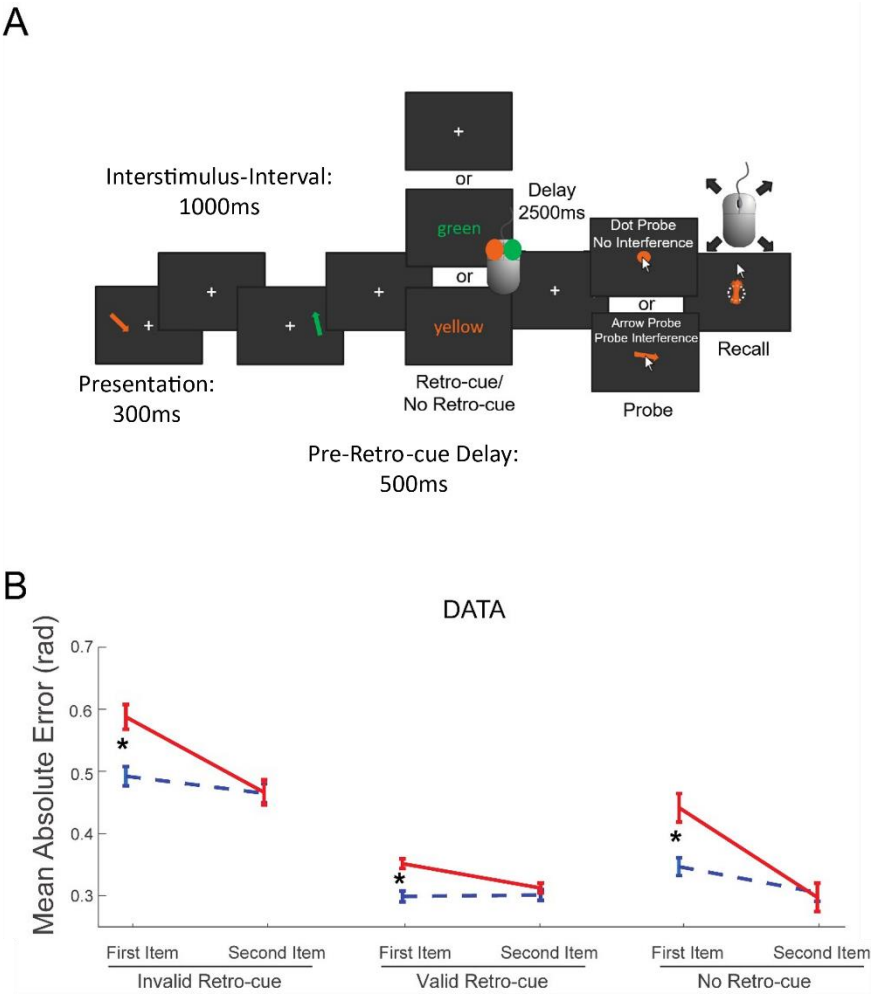


Figure 3.5 | Design and mean absolute error for Experiment 3. **(A)** The experimental task was the same as in Experiment 2 except that stimuli were presented sequentially. **(B)** Interference was modulated by sequential position (significant 2-way interaction) but not by retro-cueing (no probe-type by validity interaction). The results of post-hoc T-Tests for probe type are shown as asterisks in the graphs**.** Error bars were calculated by subtracting each subject's grand mean away from their individual per-condition values and showing the standard error (Loftus & Masson, 1994).

Discussion

The goal of this experiment was to directly compare the effect of retro-cueing and recency within a single design and assess whether they both provide protection against probe interference. Experiment 4 showed that recency and retro-cueing produced independent additive benefits, both resulting in a behavioural benefit on recall. Crucially, we confirmed the results found in Experiment 1 and 2, showing that *only* recency successfully protects items from probe interference (**Fig. 3.5**).

The data show that when the first item in a sequence is cued, and the last item is probed (i.e. the cue was invalid), although it is recalled poorly, it is remarkably still protected from interference. This strongly suggests that protection is not related to being in an active state, but rather, is related to a stronger synaptic representation.

3.8 General Discussion

The goal of the current study was to compare and contrast the prioritization of recently presented items and recently used items. In line with previous studies, the results presented here show that both recently presented items and recently used items share qualities that prioritize them over other items in working memory. We show that their effects are both strong, additive but do not interact with one another. In particular, the results suggest that the last item in a sequence is protected against interference caused by a test probe, which is not the case for a retro-cued item despite being recalled faster and more precisely in line with

previous findings (Makovski et al., 2010). We summarize the main findings for retro-cueing and recency in **Table 3.1**.

Table 3.1 | Summary of the effects seen in retro-cueing and recency

	More precise recall	Faster retrieval	Protection from probe interference
Retro-cue	Y	Y	N
Recency	Y	N	Y

Recency and retro-cue benefits add up but do not interact. One interpretation is that these two effects rely on two distinct mechanisms- interference from subsequently encoded items and attentional prioritization respectively. This supports findings in verbal memory (Niklaus et al., 2019) where the benefit the last item gains from retro-cueing is just as large as the benefit gained by the other, non-final items. Based on these findings, they suggested that the term "focus of attention" should only apply *to cued items, not the most recent item*. Instead, the last item's benefit may be better explained in terms of a continuous, yet steep gradient of precision for sequentially presented stimuli (Donkin & Nosofsky (2012), suggesting that recency does not involve attentional prioritization. The fact that the last item is especially vulnerable to interference through visual suffixes – i.e. distractors shown after encoding (Hu et al., 2014), whereas retro-cueing provides protection against visual interference (Souza & Oberauer, 2016) also points towards these two benefits relying on different mechanisms.

If recency can be abolished by distractors after encoding (Hu et al., 2014), it is not obvious then why the last item in the sequence is protected from probe interference as we show here. Importantly, our compound test probe is similar but *not* identical to a suffix, because it does not follow the sequence immediately and is part of the test-cue itself. This is an important difference, because an early suffix may be capable of producing retroactive interference causing partly overwriting the final item and reducing the recency benefit. In contrast, interference from a compound probe may instead act on a different process. Specifically, probe interference may *block reactivation* of the cued item through pattern completion (Manohar et al., 2019; Tabi et al., 2019). We had originally hypothesised that, because the last item is automatically in the focus of attention at the time of probe, it does not need to be reactivated and, as a result, is resistant to interference at the time of the probe. However, these experiments are not consistent with this hypothesis.

Pattern completion alone is insufficient to explain the protective nature of recency. Despite the fact that both retro-cued and recent items are prioritised in the sense of being more accurately reported, only the last item is resistant to probe interference. Interestingly, retro-cued items remain highly susceptible to probe interference, despite their features being recalled quicker and more precisely. This suggests that the last-item's protection from interference is established at the time of encoding and cannot be explained by attention. The benefit could be because non-final items incur partial overwriting (retroactive interference) during encoding. If encoding dominated, this explains why the last

item in the sequence is *not* susceptible to probe interference (Tabi et al., 2019) but *is* susceptible to suffix interference (Hu et al., 2014).

Moreover, the effect also cannot be explained by recency simply being stronger than retro-cueing: in Experiment 4, a valid retro-cue improved performance for non-final items even compared to performance for final items in the un-cued condition. Even though retro-cues were effective at producing improved recall, they were not able to protect non-final items from probe interference.

Previous cognitive theories ask whether benefits – like recency or prioritisation – rely on the same resource. In contrast, mechanistic neural models allow us to see that a single benefit can arise in two ways. The last item in the sequence benefits from not being overwritten at encoding by subsequent items, but also it does not need to be reactivated. Retro-cues shift the focus of attention but cannot reverse the effect of overwriting. The data suggest interference depends critically upon overwriting, yet is unaffected by the current state of activation.

In conclusion, the four experiments presented here indicate a new qualitative difference between recency and retro-cueing. The last item in a sequence is stored in a state that is robust to probe interference whereas recently relevant items are not protected from this type of interference. Recency may confer a unique kind of robustness because the last item in the sequence is not overwritten by subsequent items after its encoding.

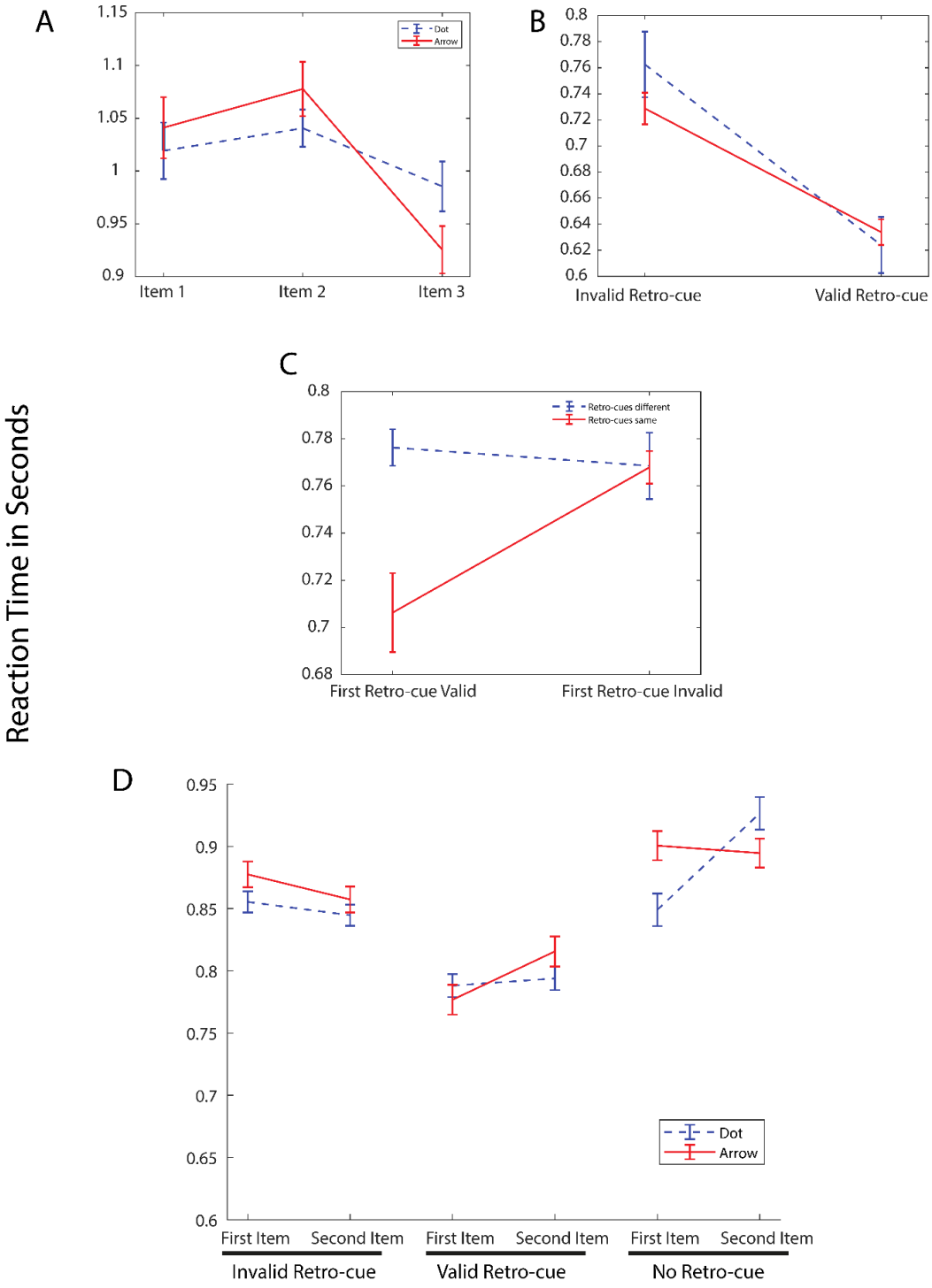


Figure S3.1 | Times to initiate responses from the moment, the probe appears on the screen. Panel **(A)** shows times for **Experiment 1**; panel **(B)** shows times for **Experiment 2**, panel **(C)** shows times for **Experiment 3** and panel **(D)** shows times for **Experiment 4. We calculated error bars by subtracting each subject's grand mean away from their individual per-condition values, and showing +/- the standard error. (Loftus & Masson, 1994).**

4. Free full report in visual short-term memory reveals that not all misbinds are swaps

4.1 Abstract

Recall errors from visual short-term memory are often not random. Rather, people may erroneously report information about the wrong item in memory. These have been interchangeably referred to as "swap errors" or "misbinding". For true swap errors, features should be incorrectly bound two ways: for the probed item as well as for the "swapee" – the other item in memory whose features are being swapped. However, previous evidence argues against true swaps, because when two features of an object have to be reported, errors are uncorrelated. Here, we demonstrate that it is possible to distinguish two mechanisms for reporting features from the wrong item: true swaps and one-way misbinding. For one-way misbinding, only one object's feature is swapped, whereas information about the other object's feature might be lost, requiring participants to guess. Previous cued recall approaches cannot distinguish these two types of error. In our free full report design, participants remembered the colours and locations of three dots shown at random locations on an imaginary circle, in random colours from a colour wheel. In cued recall, participants were cued with each of the colours, and had to reproduce the corresponding locations, or vice versa. To test free full recall, they reported both features of each object. In either case, participants reported all items in the array in self-determined order. A new mixture model was able to account for true swap errors, as well as one-way misbinding. To do this, we

introduced individual guessing parameters depending upon whether participants reported objects correctly or swapped. Furthermore, we distinguished between (i) guessing the whole object vs (ii) a feature, and between (a) guessing the swapped vs (b) non-swapped feature. Our findings show that what has previously been labelled as swap error can, in fact, be decomposed into true swap errors, or one-way misbinding.

4.2 Introduction

Being one of the most basic cognitive functions, human memory has long been in the focus of psychological research. Testing memory seems a rather simple and straight-forward thing to do. The researcher presents a participant with a defined set of information and after a delay, they ask participants to reproduce all the information. A measure so simple but efficient that it made its way into several frequently used clinical tests over the years (i.e. Mathuranath et al., 2000; Upton, 2013). Yet, this way of testing has still not made its way into visual short-term where participants are usually presented with a set of visual stimuli holding information on at least two dimensions (e.g. location, colour, orientation) and then probed by one of these dimensions. They are, for example to reproduce the location of a stimulus after being provided with a colour cue (=cued recall). In this case, the cue is not only required to solve the task at hand, but it also serves as task instruction. Retrieval, then, is posed as a one-directional problem.

A notable problem with simple accuracy measures, however, is that they might only tell one half of the full story. People might remember what features were present – such as which colours and which locations were shown on the current trial – while forgetting how the features were paired up – i.e. which colour was at which location. This extra information about the correspondence or binding between features is harder to measure. One method is to use change detection, where the task is to detect a non-matching probe display that has swapped features for a pair of objects. Thus, if the features of two objects are swapped, participants are to report the probe display as *wrong*, indicating that they know features are swapped. Through this measure, researchers can determine how well a participant binds objects into features. Yet, this remains a simple quantitative measure. More recently, continuous report measures allow modelling of these misbinding errors (Bays, Catalao, et al., 2011). If participants are presented with a cue indicating one of the items, and are required to report the corresponding feature on a continuous feature space, error can be modelled as coming from one of three possible sources. The information could originate from (i) a distribution centred around the target, (ii) around a non-target (misbinding) or, (iii) a uniform distribution in the case where participants forgot the features of all the objects (Bays, Catalao, et al., 2011; Bays, Wu, et al., 2011). This measure of misbinding errors indexes whether one object's feature is incorrectly bound to a different object (**Fig. 4.1A**). For example, if participants are presented with a target dot coloured red and two non-target dots coloured blue and yellow, they might report the blue dot's orientation instead of the orientation of the red dot.

However, reporting a single feature does not reveal the fate of the unprobed objects, or importantly, the unprobed – supposedly bound - feature. In the above example, participants might report the red dot's colour for the originally blue dot but it remains unknown if they would also report the blue colour if they were probed for the red dot (**Fig. 4.1B**). This could be seen as a symmetrical swap (or a true swap) in which two features in one dimension are actually exchanged for one another. This contrasts with asymmetrical (unidirectional) swaps, when the blue dot is reported for the red dot, but the red dot is not reported reciprocally in place of the blue orientation (**Fig. 4.1C**).

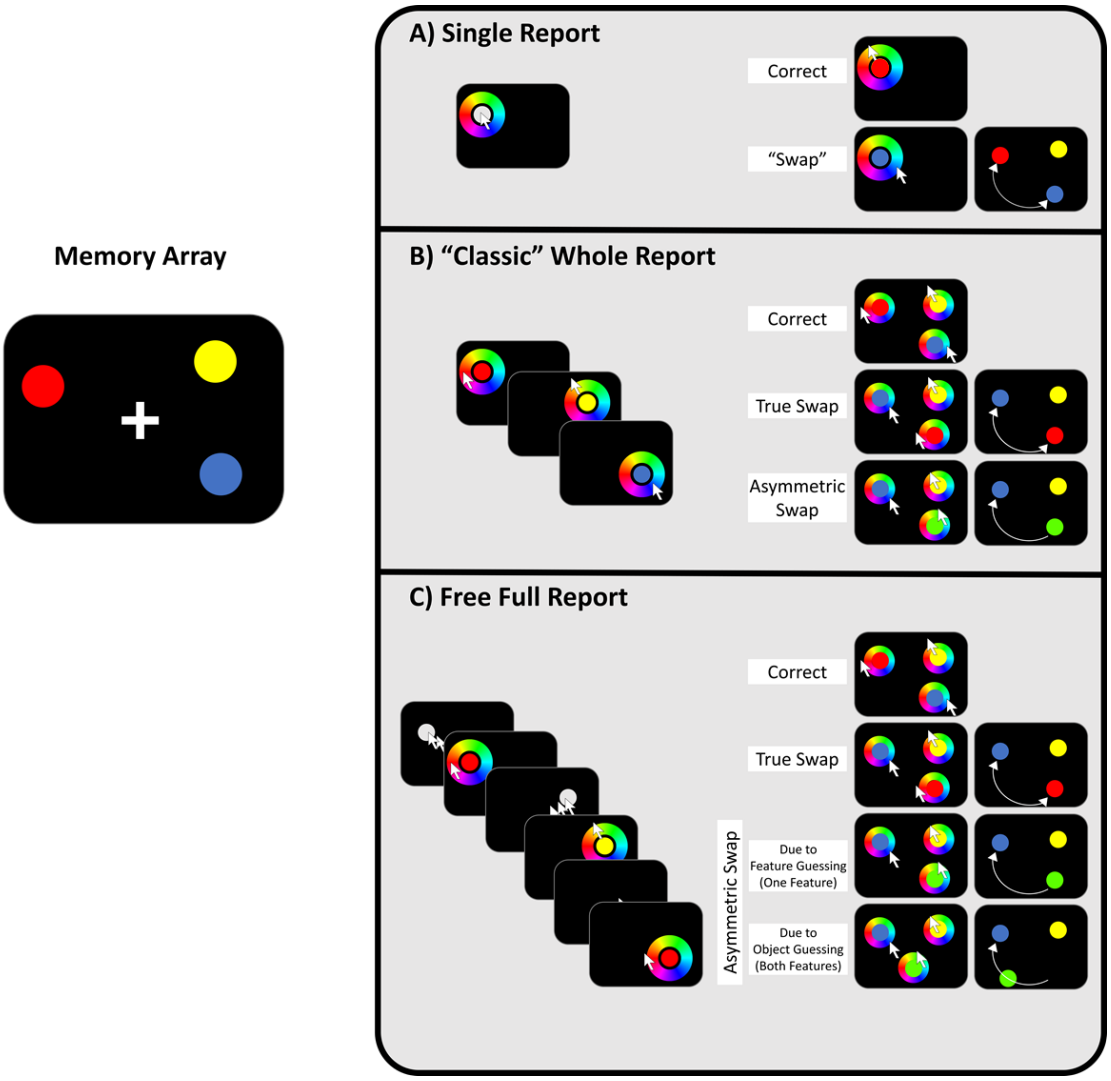


Figure 4.1 | Schematic of Swap Errors in Single Report (A), "Classic" Whole Report (B) and Free Full Report (C).

When participants are presented with a **Memory Array** of three items, there are different ways of testing their memory. In a single report study **(A),** they might be asked to only reproduce the colour of one item cued by that item's location. If they remember all features, they might either report the correct colour or another object's colour and thus do a swap error. In a whole report study **(B)**, participants are to report all features on one dimension, in this case the colour. In this case, true swap errors, in which the feature of one object is reported for another object and vice versa, can be distinguished from asymmetric swaps in which this swap only occurs in one direction. But only a free full report study **(C)** allows to assess the fate of both dimensions of the object. Thus, asymmetric swaps can be categorized as asymmetric swaps due to forgetting of one feature or of the whole object.

One way to distinguish these two kinds of swap error is to use whole report (Adam et al., 2020; Adam & Vogel, 2018; deBettencourt et al., 2019). In these tasks, for example, participants are to remember a set of coloured tiles or a set of orientations and, after a short delay, they are asked to report all of the colours or orientations they had previously seen, choosing from a set of different choices. Items reported later are recalled slower and less accurately than earlier reported items (Adam et al., 2020). One difficulty with comparing cued and whole report measures is that the order is not matched, and we sought to address this in our study by allowing freely-ordered responses in cued recall.

Though such whole report paradigms in which participants reported all items can quantify capacity precisely, they still cannot address the critical question of whether swaps are really symmetrical. If a feature to be reported was forgotten or misattributed to another object, these tasks do not provide data on what happened to the other features on the *cue* dimension. Thus, full object forgetting cannot be assessed, even in a whole report paradigm.

Recent evidence, however, suggests a need for a paradigm that allows us to distinguish between symmetric and asymmetric swaps, as well as between single-feature versus whole-object forgetting. For example, Pratte (Pratte, 2019) argues that non-target responses might in fact be strategic guesses. In his paradigm, the author probed participants by colour and asked them to report the respective location of that colour, in addition to making a confidence rating of their response. He finds two different types of non-target responses, with high versus low confidence responses. In fact, only low confidence non-target responses were

evenly distributed relative to the probed colour, suggesting uniform guesses. However, in high confidence non-target responses and in line with interference models of retrieval (Oberauer & Lin, 2017), the incorrectly reported location was reported closest to the non-target that was categorically closest to the target on the probe dimension. Hence, probe modalities can in fact cover up guessing if only one dimension is reported at a time. Moreover, non-target responses are most common in low confidence trials compared to high confidence trials (Rademaker et al., 2012), suggesting that misbinding is in fact not a highly confident response due to a supposed exchange of feature representations.

Some recent accounts go one step further and suggest that the observed distinction between target responses and supposed random guesses can be fully explained by the level of psychophysical similarity among items in memory (Schurgin et al., 2020). In this target confusability competition model, the memory signal strength together with the familiarity between target and foil(s) are sufficient to explain imprecision and guess rate in previously published experiments. Thus, if a foil stimulus at retrieval is very different to the target (i.e. 180° on continuous angular space), the participant is more likely to respond to select the target as there is hardly any similarity between foil and target. However, with foils (or parts of a colour or orientation wheel, for example) that are closer to the target, there is a nonlinearly increasing similarity to the target. Consequently, the discrimination between guessing and target response could be explained by the signal strength of the target stimulus only.

One way to measure swaps is to ask participants to report two features of the same object. In this situation, forgetting one dimension of an object is only weakly coupled to forgetting of the other dimension, suggesting that forgetting afflicts individual features more often than whole objects (Bays, Wu, et al., 2011). This would be in keeping with the existence of either symmetrical or asymmetrical swaps, and so does it not distinguish these scenarios.

Here in two experiments, we introduce a novel method of free full report that allows participants to reproduce *all* features of *all* objects, in the absence of a cue. Together with a new statistical model of sources of error, this enables us to unravel symmetric swap errors versus asymmetric swaps, and feature versus object guessing in short-term memory.

Such model also allows further investigation of very recent findings in the field of feature binding: Heuer (Heuer et al., 2016; Heuer & Schubö, 2016) and colleagues and Schneegans and Bays (Schneegans & Bays, 2017) found evidence for differential mechanisms involved in spatial as opposed to feature-based selection in visual STM. They argue that non-spatial information such as a colour or an orientation are remembered indirectly through space as they are bound into an object by sharing space in the spatial dimension. The authors conclude that there is a special role of location in visual STM in comparison to other features that are not bound directly but only through location. So, asking participants to either first reproduce and thus remember the colour or the location of an object might – in a free full report study – have a significant effect on participants' performance. Maybe when asked to remember the colour of one of the objects, participants

indirectly go by the location which could lead to higher levels of error compared to conditions in which they are first asked to remember the location and then the colour. Thus, the free full report study here investigates both experimental scenarios.

Another dimension that is particularly important for binding is time. If stimuli are presented simultaneous, competition between features could be increased and symmetrical swaps might occur more frequently. The sequential presentation of items could, on the other side, be interpreted as an additional attention manipulation above the task itself. Thus, interference could particularly occur in sequential experiments and participants could perform significantly worse with the sequential presentation of items. There are several studies finding error rates to be either higher in sequential (Allen et al., 2006; Brown & Brockmole, 2010) or in simultaneously presented arrays (Fougnie & Marois, 2009; Ihssen et al., 2010) in comparison to the other. The changes in symmetrical and asymmetrical swaps could be particularly informative to that debate.

In summary, we hypothesise that there are asymmetric as well as symmetric swaps. We furthermore aim to explore differences in these swap types between simultaneously and sequentially presented items and if participants are to first reproduce the location or the colour of an object.

4.3 Methods

Participants

For EXPERIMENTS 1-2, two individual sets of 20 participants were recruited. Inclusion criteria were the age range of 18 to 30 and being neurologically normal. Participants were invited for two one-hour sessions that were to take place within a period of seven days. In EXPERIMENT 2, the 20th participant was not able to perform their second session due to a general lockdown imposed by the British government over the global health incident related to COVID-19. Their data was therefore excluded for analysis.

Stimuli

EXPERIMENT 1 and 2: Free full report

Participants were presented with stimuli at a viewing distance of approximately 60 cm on a 24-inch LCD monitor. Three dots (radius of 0.7° of visual angle) on a black background were presented in three randomly chosen locations along the boundary of an imaginary circle with a radius of 6.5° around fixation. The dots' angular position on the circle were pseudorandomly chosen from a uniform distribution between 0 and 2π radians. If the initially in this way assigned angles would have led to two or more dots overlapping (minimum distance of 1.4° of visual angle), another three random angles were drawn until no two dots would overlap. Colours of the three dots were taken from a continuous colour wheel with 100% saturation and 100% brightness (HSV) and a colour hue value randomly

drawn from a uniform angular space (0 to 2*π), the same way the location angle was determined. There was a minimum hue angular separation of 5° between the colours of the three dots implemented to avoid colours being indistinguishable for participants.

Procedure

The main difference between the first and second experiments was that the three coloured dots were presented simultaneously in the first experiment for a period of two seconds. In the second experiment, however, participants were presented with each dot for a period of 500ms followed by an inter-item blank of 500ms. In both experiments, the memory array was followed by a blank black screen of 4000ms. After this delay, participants were probed in four different ways (**Fig. 4.1**) - cued by colour, cued by location, or uncued, with either location first or colour first:

i) **Cued by colour:** Three squares (radius of 0.7° of visual angle) in the colours of the three original dots appeared at a distance of 1.6 ° of visual angle- from the screen centre each. These squares were equally spaced-out around the boundaries of this imaginary circle, starting from a random offset in a random order. Participants were asked to click on one of the squares, indicating which colour's location on the imaginary circle they wanted to report. After they clicked on the chosen square, all squares disappeared, and a central white pentagon appeared as a fixation at the screen centre. Throughout the whole

experiment, this pentagon at fixation indicated that participants could choose a location. As soon as participants started moving the mouse, the pentagon disappeared and a dot in the colour that was selected appeared on the original imaginary circle at the angle the mouse cursor pointed towards, no matter whether the cursor was within or outside of the imaginary circle's boundaries. The dot changed its location on the imaginary circle according to the cursor position until a mouse button was clicked to confirm the location choice. After they clicked, participants went back to the screen on which they selected the first square. Now, however, the previously selected square was not shown, and participants selected from the two remaining squares. This process was repeated until all three locations were reported.

ii) **Cued by location:** Three dots were presented on the original imaginary circle in the original target locations, however, coloured in light grey (RGB [211 211 211],). As soon as participants started moving the mouse, a cross appeared on the boundary of the circle at the angle the mouse cursor pointed towards, measured from the screen centre. Once the cross touched one of the three dots, participants could click a mouse button to confirm their location selection. After clicking, a colour wheel of 8.6° of visual angle appeared in the screen centre that was a visual representation of the colour space the stimuli colours were drawn from. The colour wheel was randomly rotated in each trial. As soon as participants started moving the cursor, the selected dot started changing its colour according to the angle from the screen centre in

relation to the colour wheel. By clicking a mouse button, participants confirmed their colour choice. As in i), this procedure was repeated until all colours were presented.

iii) **Uncued, location then colour:** Participants were presented with the pentagon that indicated they could choose a location by moving the mouse like in **i**. After they confirmed the location by clicking a mouse button, they were presented with the colour wheel and chose a colour for the chosen location like in **ii**. Again, this was repeated for the other two responses.

iv) **Uncued, colour then location:** Participants were first presented with the colour wheel at the screen centre (see **ii** and **iii**) and a light-grey dot (RGB [211 211 211]) in its centre. Once participants started moving the mouse, the dot's colour changed like in **ii** and **iii** and participants could confirm their final colour selection by clicking a mouse button. Once they confirmed this selection, the appearing pentagon at fixation indicated that they could choose a location. As in **i**, a dot reflecting in the chosen colour appeared on the original imaginary circle that changed its location according to the cursor's angle from the screen centre. This procedure was repeated until three dots were reproduced from memory.

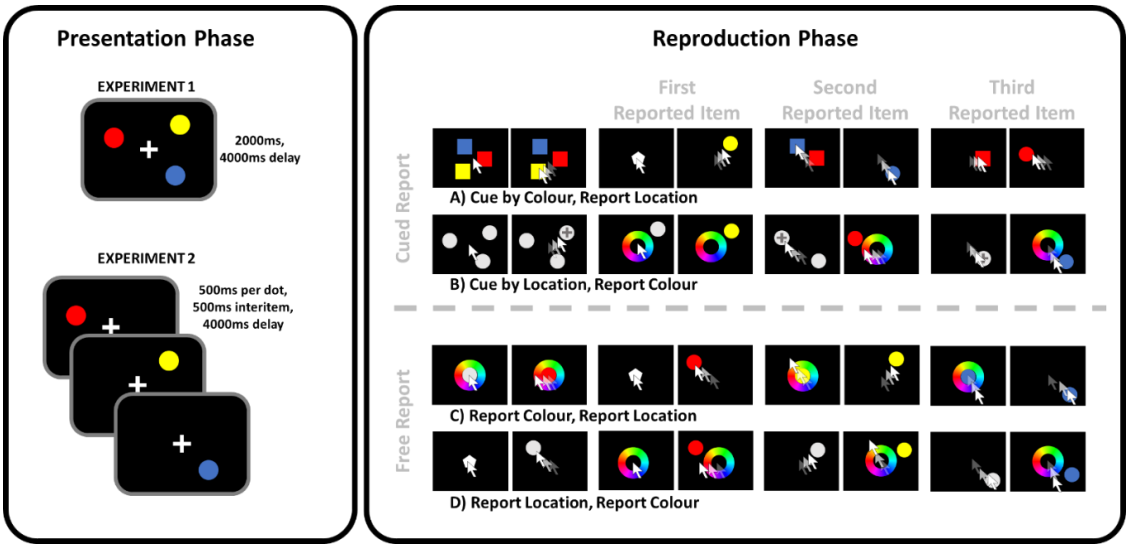


Figure 4.2 | Design of Experiments 1 and 2. In Experiment 1, participants were presented with three coloured dots simultaneously for a period of 2000 ms and in Experiment 2 sequentially for a period of 500 ms per dot and an inter-item delay of 500 ms. After a delay of 4000 ms, participants reported the items. In all conditions, participants reported all three items, on both dimensions, in a freely-chosen order. They were either presented with a cue (Reproduction Phase: top half, "Cued Recall") or were to reproduce the array without a cue (Reproduction Phase: bottom half, "Uncued Recall"). In case of cued recall, participants were either presented with three squares in the colour of the previously seen stimuli **(A)** or with three dots in the locations of the originally presented array **(B)**. They were able to choose for which one of the three cues for which they want to reproduce the respective target dimension (colour or location) by clicking on it. As soon as they clicked on one of the three cues, they disappeared, and they were able to either place the selected colour on the memory array's imaginary circle or to colour the selected location using a colour wheel. In the uncued recall trials, they either started off witch a colour wheel **(C)** and coloured a dot in the centre of the screen or they placed a dot on the boundaries of the circle **(D)**. Afterwards, they completed the response on the other dimension.

Analysis

The primary aim of this analysis is to match responses to display features, so that we can ascertain 1) whether misbinding errors occuring when reporting one object are coupled to reciprocal misbinding errors in the other object (symmetrical swaps), and 2) whether people swap both features of an object together (object swaps).

The absolute error of recall was defined as the unsigned difference between target and response angles. This absolute error was compared between conditions using repeated-measures ANOVAs.

Reaction Times were measured as the time between the moment a response was possible, and the moment the response was actually initiated with the mouse.

Probabilistic Free full report model

A new Bayesian hierarchical model was introduced to account for the sources of error in memory.

In summary, the model estimates a distribution across the possible orders in which participants report the three items, and accounts for each response as a mixture of veridical responses, swaps with one-feature reported from another object with a reciprocal swap, or without a reciprocal swap. Complete guesses arise where a feature is *completely* forgotten and not reported for any of the items. The model

also accounts for three-way (cyclic) swaps, and the possibility of correlated guessing for features within an object.

Here we describe the generative model of participants' responses, fitted by Gibbs sampling. Given that in the uncued condition, the order in which participants reproduced the shown stimuli was unknown, the first step was to choose from one of the six possible permutations of the reproduction order ABC (ABC; ACB; BAC; BCA; CAB; CBA). The probability was drawn from a categorical distribution with six categories representing these permutations.

ReproductionOrder ~ dcat(c(1/6, 1/6, 1/6, 1/6, 1/6, 1/6))

Next, the model drew from a categorical distribution whether participants made a swap error (P_{swap}), a cyclic swap (P_{cyclic_swap}) or neither ($1 - P_{swap} - P_{cyclic_swap}$).

swaptype ~ dcat(1 - P_swap - P_cyclicswap, P_swap, p_cyclicswap)

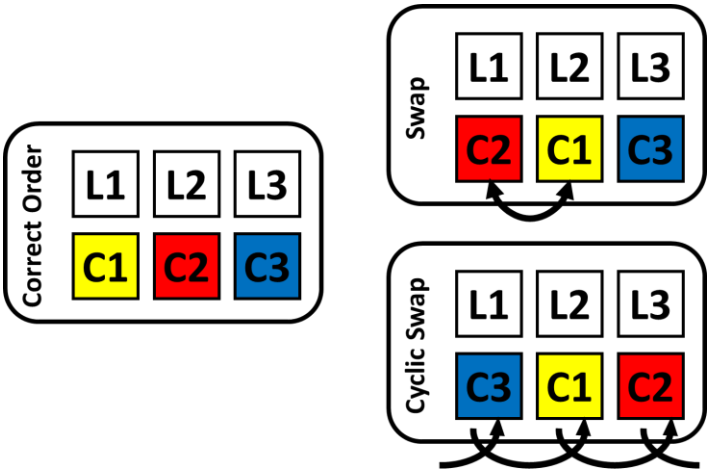


Figure 4.3 | Schematic of Swap and Cyclic Swap Errors. The correct order of reported features is depicted on the left side. Locations one to three (L1-3) and colours one to three (C1-3) were to be reported by the participant. In swaps, two features on one dimension, colour in this example, are exchanged for one another. In cyclic swaps, all features of one dimension are shifted along the other dimension.

In swap errors, participants exchange two features on the same dimension of two different objects for one another. Without a swap, location 1 (**Fig. 4.4: L1**) was to be reported with colour 1 (**Fig. 4.4: C1**), location 2 with colour 2 and location 3 with colour 3. If participants make a symmetrical swap error, they report location 1 with colour 2 and, respectively, location 2 with colour 1 (**Fig. 4.4, right top**). A double swap may lead to a cyclic three-way swap, moving *all* three items on one dimension e.g. reporting location 1 with colour 3, location 2 with colour 1 and location 3 with colour 2 (**Fig. 4.4, right bottom)**.

When a swap occurs, the model applies one of the three possible swap and one of the two possible cyclic swap combinations,

Swapnumber ~ dcat(c(1/3, 1/3, 1/3))

Cyclswapnumber ~ dcat(c(1/2, 1/2))

rearranging the responses to the combination that matches the data best. Another way of forgetting is a response drawn from a uniform distribution, a guess. The model accounted for participants making guesses on either one (feature guess) or both features of an object (object guess). These were drawn from a Bernoulli distribution indicating whether the information was either drawn from a von-Mises or a uniform distribution (**Fig. 4.5**).

Feature_Guess ~ dbern(G_feature_guess)

Object_Guess ~ dbern(G_object_guess)

To account for asymmetrical swaps, we allow one of the swapped items to incur *additional* guessing, over and above the baseline guessing above. In other words, we add a guessing term that is specific to items that have been swapped. Again, this could affect both features of the object, or just one of the two features.

Feature_Guess_Swap ~ dbern(G_feature_guess_swap)

Feature_Guess_CyclicSwap ~ dbern(G_feature_guess_cyclicswap)

Object_Guess_Swap ~ dbern(G_object_guess_swap)

Object_Guess_CyclicSwap ~ dbern(G_object_guess_cyclicswap)

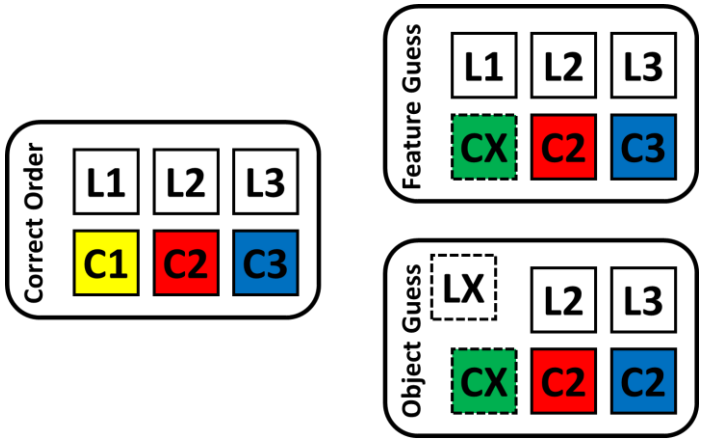


Figure 4.4 | Schematic of feature and object guesses. In feature guessing, participants report a random feature (in this example the colour green) instead of the original feature. In object guessing, both features of an object are forgotten by the participant. I.e., in this example, they neither remember the colour nor the location of the first object.

Within trials including a swap, the model makes a difference of whether the guessed feature/object is part of the swap or the feature/object otherwise unaffected by the swap itself. If, based on the data, the model determines a feature or both features of an object to be a guess, the feature/s is/are assumed to be drawn from a uniform distribution. Otherwise, the response is assumed to be drawn from a von-Mises distribution around the target feature.

Response ~ dvonmises(Target, z*precision)

where z is a logical defining whether the response is drawn from a von mises distribution around the target or from a uniform distribution in circular space.

Similarly, the logarithmic likelihood was calculated using the logarithmic von-Mises distribution (dlogvonmises).

Swaps in which information about two objects is symmetrically exchanged are true, symmetric swaps (**Fig 6**). If, however, information is only exchanged on one side of the swap, and on the other side, there is a feature or a whole object guess, the swap is asymmetrical.

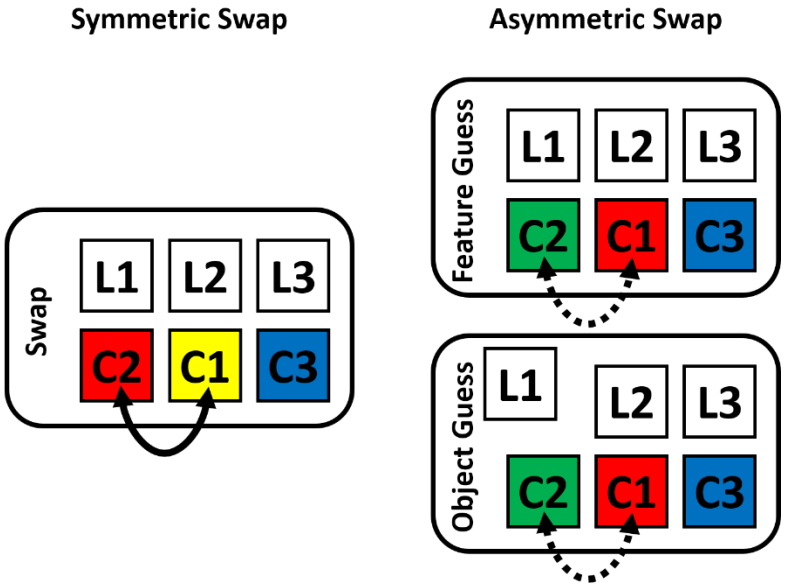


Figure 4.5 | Schematic of symmetric and asymmetric swap errors. In symmetric swap errors (**left**) information on one dimension is equally exchanged between two objects. However, if there is feature or object guess involved in one of the swapped features, the swap error becomes an asymmetric guess (**right**).

The parameters presented here (proportion of swaps, cyclic swaps, feature guessing, object guessing and of precision for colour and location) were estimated per subject, along with the subject mean and the between-subject variance by the model. All of these parameters were allowed to vary between cued trials and the *Colour First* and *Location First* uncued conditions. The number of model

adaptations was set to 5000, iterations were set to 10000 and the number of chains was set to 4 resulting in a total of 40000 samples. Participants means for each volunteer were averaged over these 40000 samples.

In summary, the reasoning behind including cyclic swaps is that two swaps within the same trial could possibly lead to either reversing the swap or to two swaps which will be represented by a cyclic swap. Naturally, guessing can lead to forgetting of one feature or the whole object which is represented by two categories of guesses. This model uniquely implements different guessing parameters for trials without a swap, trials with one swap and trials with a cyclic swap. The reasoning being that with different ways of disruption to mental binding representations would lead to different likelihoods of guessing. I.e., here it is hypothesised that one swap is more likely to be accompanied by guessing than a trial in which no swap occurs. Moreover, a trial with two swaps (cyclic) swap should in turn show a higher probability of guessing. Thus, the model builds on the idea of memory errors being related to one another and does not assume asymmetric swaps to simply be swaps with subsequent forgetting. Furthermore, the model allows to directly observe binding by testing both dimensions of one object.

4.4 Results

EXPERIMENT 1: Free full report of simultaneously presented stimuli

Mixture Model of Responses

When all trials were fit, the presented model (WAIC = 18203.05) showed a better fit than a null model without swap errors or guessing (WAIC = 29078.96). A model that did not make a difference between the swapped and non-swapped items in terms of guessing showed the better fit (WAIC = 18106.77).

Models that allowed factors “cued versus uncued” recall but not “location versus colour first within uncued recall” to have an effect on all components showed a better fit (WAIC = 18137.07) than those models that allowed both (WAIC = 18203.05) or the latter but not the former (WAIC = 18261.55) to have an effect on the model components.

Precision for location was numerically higher in the Location First (Uncued) compared to the Colour First (Uncued) condition (17.56±5.34 vs. 14.32±5.03; **Fig. 4.7, posteriors in Fig. 4.8**) and Cued condition (14.82±4.94). It was also numerically higher in the Cued compared to the Colour First (Uncued) condition.

Precision for colour was numerically higher in the Cued compared to the Colour First (Uncued) condition (10.94±2.70 vs. 9.96±2.69) and the Location First (Uncued) condition (9.66±2.81). The precision for colour was also higher in the Colour First (Uncued) compared to the Location First (Uncued) condition.

Evidence was found for both symmetrical and asymmetrical swap errors (**Fig. 4.7**). Across the cued conditions, swap errors had an estimated probability of 15.44% (SD = 5.81%). Because the identity of one feature of each object is known with certainty, this condition shows more swaps. This contrasts with the uncued conditions, with 2.99% (SD = 1.31%) swaps when participants first reproduced colour and 2.91% (SD = 1.49%) when they first reproduced location. For the two uncued conditions, the model further revealed that 42.822% (SD = 5.95%) and 62.94% (SD = 5.5%) of swaps respectively were symmetrical swaps.

Swaps could be asymmetrical either due to forgetting of just one feature or due to forgetting of two features and thus the whole object. 29.76% (SD = 6.16%) and 13.36% (SD = 2.95%), respectively, of all swaps were asymmetric due to forgetting of one feature and 27.41% (SD = 1.46%) and 23.69% (SD = 2.61%), respectively, were asymmetric due to forgetting of one whole object.

Cyclic swaps arose with a frequency of 4.70% (SD = 6.67%) in cued trials, 1.73% (SD = 2.57%) in Colour First (uncued) and 1.22% (SD = 1.61%) in Location First (uncued) trials.

In summary, there was not only evidence for the co-existence of symmetrical and asymmetrical swap errors but their contribution to the overall number of swaps is impacted on by the order in which participants are to reproduce the features of an object. I.e., when participants are to reproduce the colour of an object first, this benefits their precision for colour over conditions in which they are to reproduce the location first. Yet, there is generally lower precision for location in the *Colour*

First condition. Within swaps, the proportion of asymmetric swaps is higher in the Colour First condition compared to the *Location First* condition. Overall, the WAIC generally prefers a model that does not make a difference between the two uncued conditions and a model that makes no difference between guessing in swapped and non-swapped items.

Absolute Error

A 3x6-ANOVA of sequential report position (first, second, third reported object) and probe type (Uncued – Location First: Location; Uncued – Location First: Colour; Uncued - Colour First: Location; Uncued - Colour First: Colour; Cued: Location; Cued: Colour) was conducted to investigate whether the order in which participants reported objects and features had an impact on their absolute error in radians (**Fig. 4.9**). A main effect of sequential report (BF_{incl} = InF) suggested that participants reported the best remembered object first and the worst remembered object last. In addition, there was a main effect of the probe modality (BF_{incl} = Inf) and an interaction of both main effects (BF_{incl} = 16.52) which was followed up using Holm-corrected t-tests (**Supplementary Table 4.1**). The highlights of this analysis are that i) participants performed significantly better in the uncued compared to the cued conditions, ii) location responses benefitted from this effect more than colour responses and iii) within the uncued condition, participants perform better if first probed for the location.

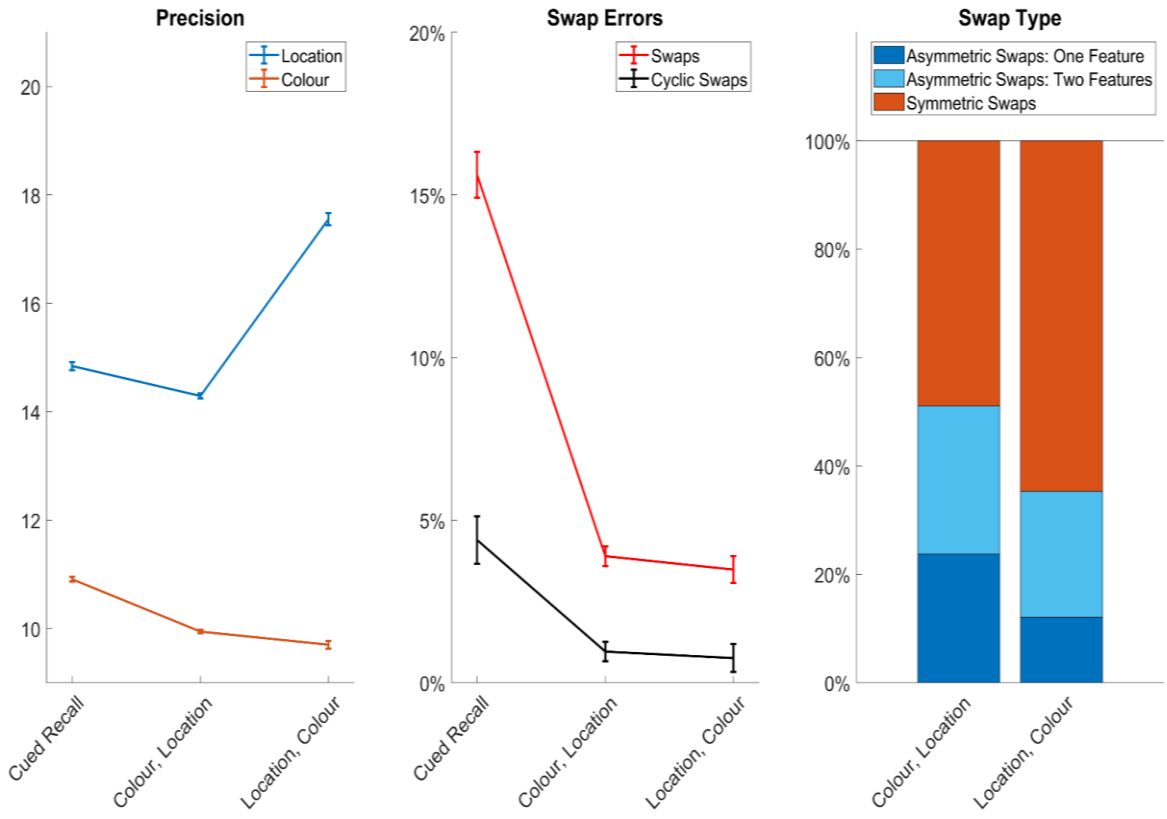


Figure 4.6 | Precision (left), swap errors (middle) and types of swap errors (right) for Experiment 1. Swapping was increased in cued conditions. The model further allowed us to distinguish between symmetric and asymmetric swaps. There was strong evidence for the co-existence of symmetric and asymmetric swaps. In the *Colour First* condition, participants were significantly more precise for colour, yet they produced more swap errors than in the *Location First* condition. Asymmetric swaps occurred more often in the *Colour First* condition. The error bars were calculated by subtracting each subject's grand mean away from their individual per-condition values and showing ± the standard error (Loftus & Masson, 1994).

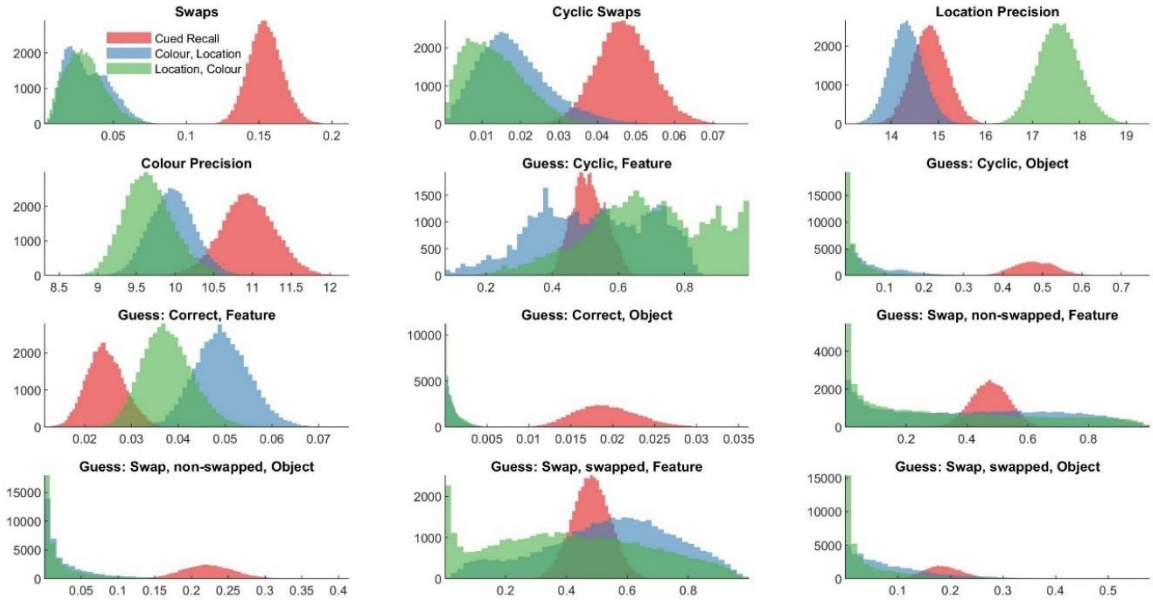


Figure 4.7 | Plots of Posterior Distribution of all free parameters.

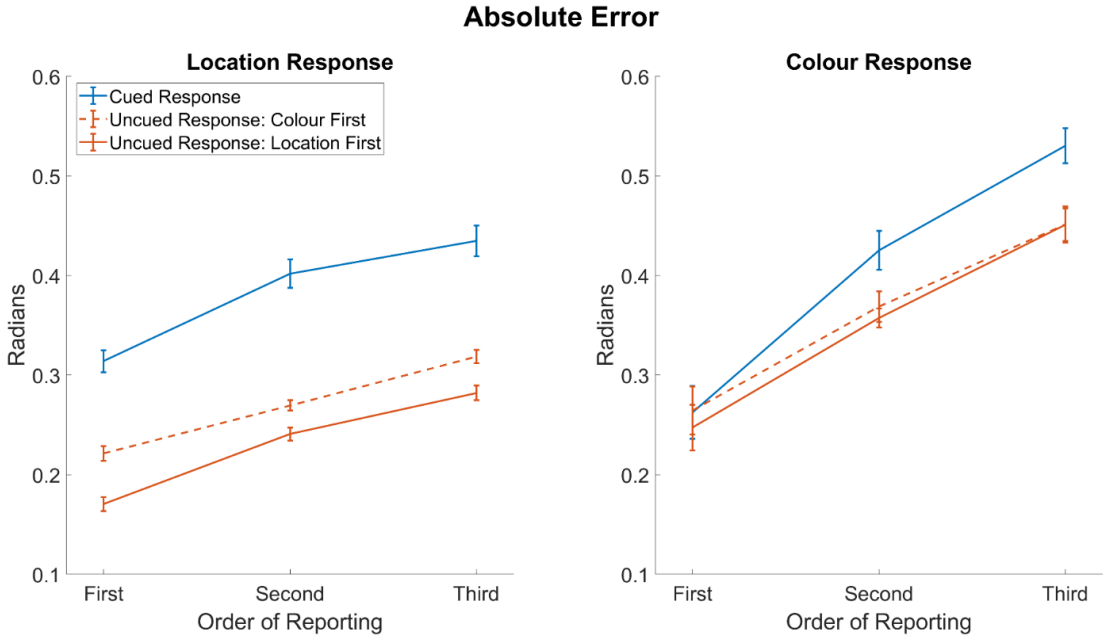


Figure 4.8 | Absolute error in radians between response and target for the cued (left) and uncued recall (right) conditions in Experiment 1. Participants perform better in uncued compared to cued conditions. This benefit was greater for location responses. There was also a benefit for when the location was reported first.

EXPERIMENT 2: Free full report of sequentially presented stimuli

Mixture Model of Responses

As for Experiment 1, the full model had a better fit (WAIC = 7857.40) than the null model without guessing or swaps (WAIC = 17479.97).

As in Experiment 1, models that allowed factors "cued versus uncued" recall but not "location versus colour first within uncued recall" to have an effect on all components showed a better fit (WAIC = 7808.) than those models that allowed both (WAIC = 7857.40) or the latter but not the former (WAIC = 7817.62) to have an effect on the model components. Notably, if guessing in swapped and non-swapped features and objects was set to be equal, models had a worse fit (WAIC = 7949.21). Thus, in sequential recall, it mattered whether a feature or object was swapped in terms of guessing probability, as opposed to findings in the first experiment.

Confirming results of the first experiment, precision for location was numerically higher in the Location First (Uncued) compared to the Colour First (Uncued) condition (20.36 (SD = 4.34) vs. 16.65 (SD = 4.25); **Fig. 4.10, posteriors in Fig. 4.11**) and Cued condition (18.45 (SD = 4.22)). It was also numerically higher in the Colour First (Uncued) compared to the Cued condition.

In this experiment, precision for colour follows the same pattern as precision for location, that is, it was numerically higher in the Location First (Uncued) compared

to the Colour First (Uncued) condition (13.75 (SD = 3.36) vs. 12.49 (SD = 3.29)) and Cued condition (13.06 (SD = 3.24)). It was also higher in the Cued compared to the Colour First (Uncued) condition.

Swap errors occurred at a frequency of 17.11% (SD = 7.04%) in the cued condition. Again, participants made less swap errors in the Location First (Uncued) condition compared to the Colour First (Uncued) condition (5.87% (SD = 4.02%) vs. 7.35% (SD = 4.63)).

There were numerically more symmetric swaps in the Location First (Uncued) condition (67.97%, SD = 6.88%) than in the Colour First (Uncued) condition (37.64%, SD = 11.86%) but fewer asymmetric swaps with guessing on one feature which occurred significantly less in the Location First (Uncued) condition (9.54%, SD = 2.29) compared to the Colour First (Uncued) condition (9.54%, SD = 2.29%). Numerically, the two uncued conditions were similar in terms of asymmetric swaps based on guessing of the whole object (Colour First: 23.19%, SD = 2.84% vs. Location First: 22.49%, SD = 4.62%).

There were comparable levels of cyclic swaps in the Location First (unced) condition (0.27%, SD = 0.58%) compared to the Colour First (uncued) condition (0.29%, SD = 0.38%). Cyclic swaps occurred at a frequency of 3.10% (SD = 1.93%) in cued trials.

As opposed to the first experiment, there is no benefit for participants' precision for colour in the *Colour First* condition anymore. In the sequential experiment, this condition rather shows to produce more swaps and lower precision in comparison to the *Location First* condition. The asymmetric swap proportion is also increased

in this condition, further confirming that location might be asymmetrically bound to other features and thus confirming earlier findings from Heuer et al. and Schneegans et al.

Detailed plots for individual guessing parameters can be found in **Supplementary Fig. 4.2**.

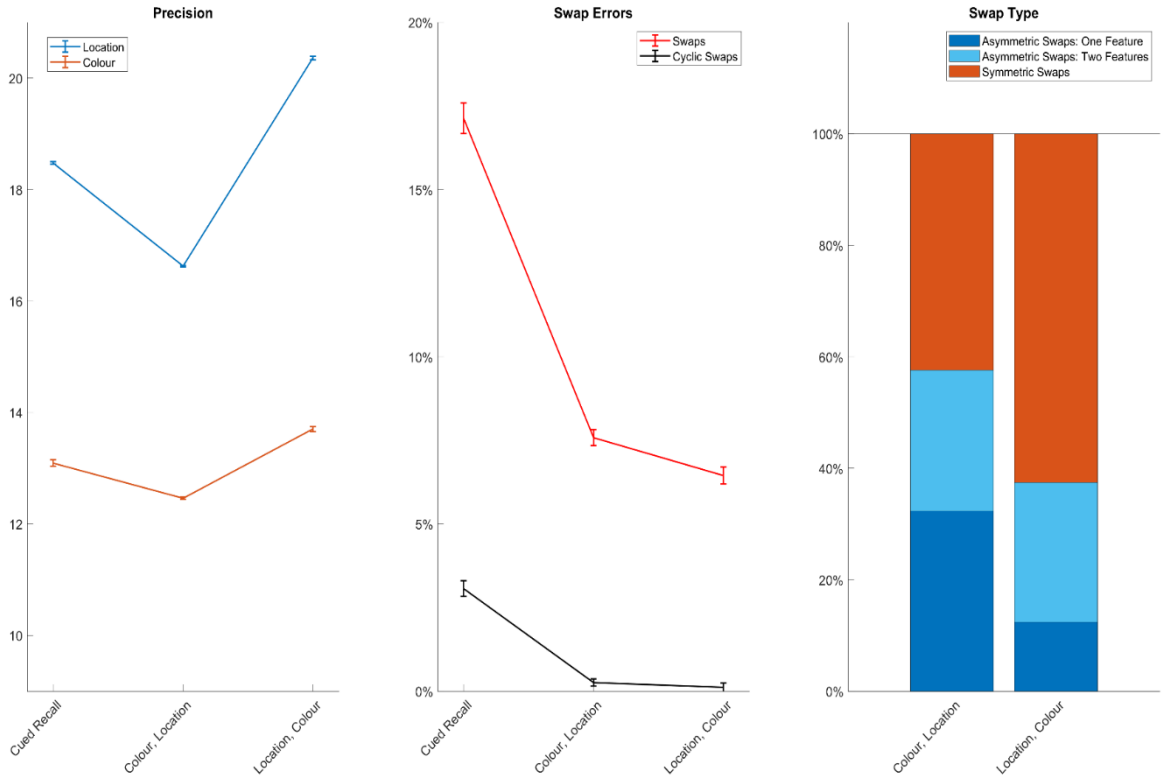


Figure 4.9 | Precision (left), swap errors (middle) and types of swap errors (right) for experiment 2. Reproducing the main results of the first experiment, swap errors happen more often in cued conditions. Again, there was strong evidence for the co-existence of symmetric and asymmetric swaps. Within the uncued conditions, symmetric swap errors were more frequent in Location First (Uncued) compared to Colour First (Uncued) conditions. In this experiment, as opposed to the first experiment, were worse in both precision measures in the *Colour First* condition compared to the *Location First* condition. Asymmetric swaps occurred more often in the *Colour First* condition. The error bars were calculated by subtracting each subject's grand mean away from their individual per-condition values and showing ± the standard error (Loftus & Masson, 1994).

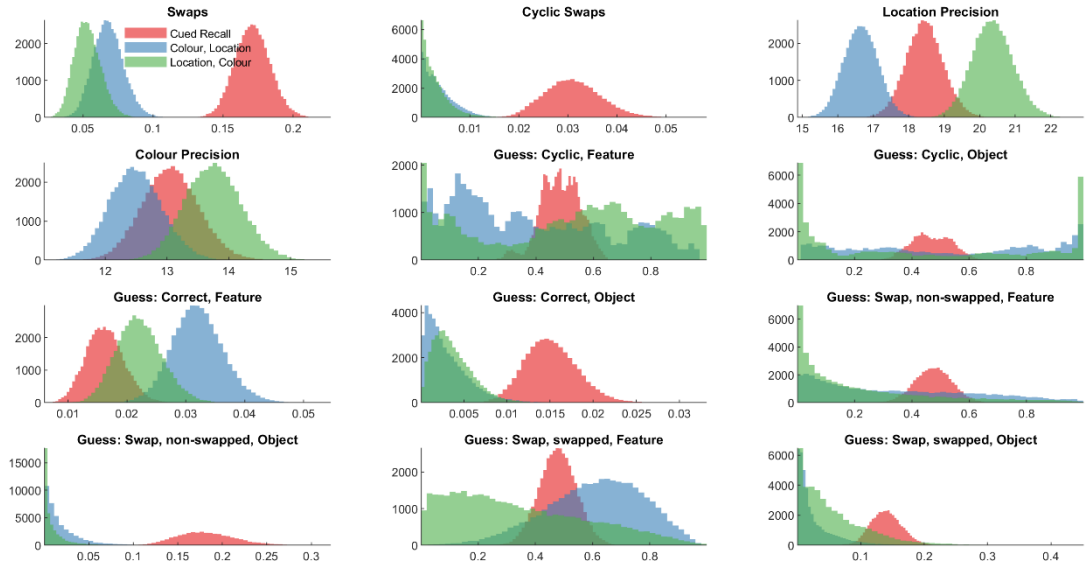


Figure 4.10 | Plots of Posterior Distribution of all free parameters.

Absolute Error

As in Experiment 1, we performed a 3x6-ANOVA of sequential report position (first, second, third) and probe type (**Fig. 4.12**, Uncued – Location First: Location; Uncued – Location First: Colour; Uncued - Colour First: Location; Uncued - Colour First: Colour; Cued: Location; Cued: Colour). Replicating the results of the previous experiment, there was a main effects of the sequential report position (BF_{incl} = Inf) suggesting that participants reported the worst remembered item last. In addition, there was a main effect of the probe type (BF_{incl} = Inf) and post-hoc t-tests showed that there was in fact a significant difference between all six different kinds of reports (**Supplementary Table 2**). Again, the highlights of this clear hierarchy are that i) participants performed significantly better in the uncued compared to the cued conditions, ii) this benefit is greater for the location than for the colour condition and iii) within the uncued condition, participants perform better if first probed for the location. There was no evidence for an interaction of both factors (BF_{incl} = 0.58).

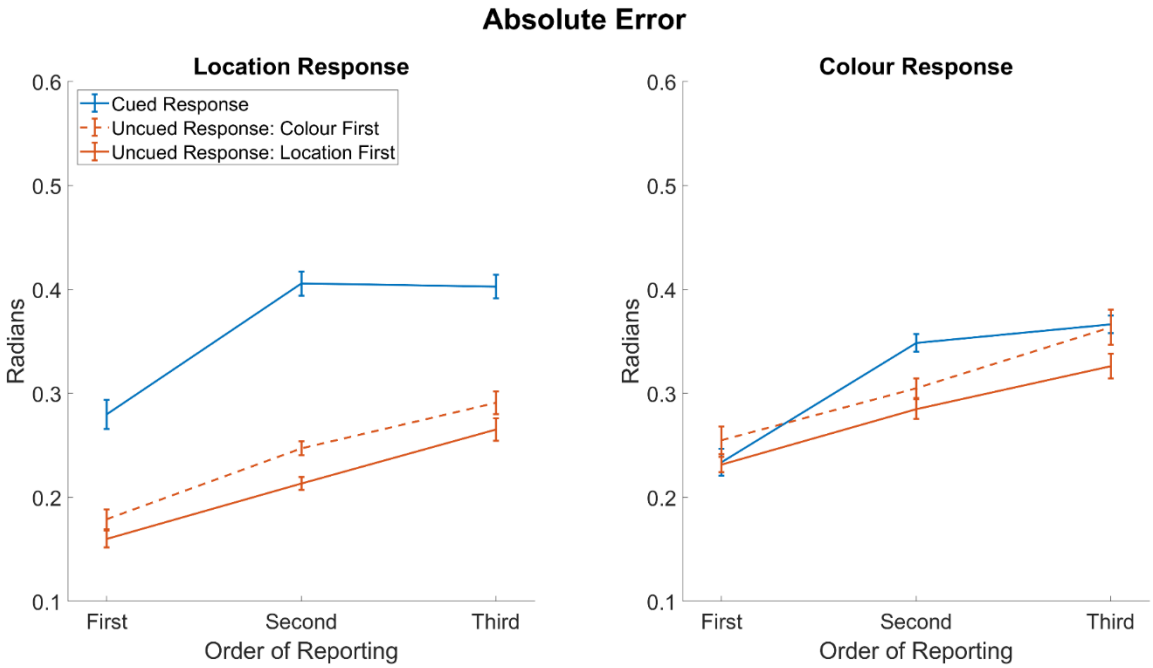


Figure 4.11 | Absolute error in radians between response and target for the cued (left) and uncued recall (right) conditions in Experiment 2. As in Experiment 1, participants perform better in uncued compared to cued conditions. This benefit was greater for location responses. There was also a benefit for when the location was reported first.

Order of Reproduction

The order in which participants reproduced the memory array was investigated (**Fig. 4.13**) using a 6x6 repeated-measures ANOVA of the six permutations 1 2 3, 1 3 2, 2 1 3, 2 3 1, 3 1 2 and 3 2 1 and the four probe conditions, whereby the likely order in the uncued conditions was – like in the absolute error – based on the smallest distance ("Dist Model") taking colour and location into account or extracted from the full probabilistic model ("Prob Model").



Figure 4.12 | Order in which participants reproduce the sequential memory array where "1 2 3" is the order in which they have originally seen the stimuli appear on the screen. In the cued conditions, the order was extracted from the data but in uncued conditions, it was either calculated using the minimum distance (Dist Model) or the full probabilistic model (Prob Model). A clear preference of the order "1 2 3" was consistent over all conditions and models.

The results showed a main effect of reproduction order (BF_{incl} = 1.72e+13) but not of probe type (BF_{incl} = 6.35e-4). Post-hoc Holm-corrected t-tests (**Supplementary**

Table 3) showed that participants preferred the combination “1 2 3” by far over any other combination. The combination “1 3 2” was preferred second over the other four combinations. This suggests a strong preference for an order of reproduction that is identical to the order of presentation. The second most preferred combination also starts off with the firstly presented item. Any of the other chosen orders of reproduction is hardly used in more than two of 50 trials per condition on average.

Furthermore, the results suggest that both, a simple model of the smallest distance, as well as the probabilistic model predict the correct order of reproduction well.

There was no evidence for an interaction of both main effects (BF_{incl} = 3.45e-5).

Parameter Recovery

In order to explore the how well model parameters reflect the data, the model was run on synthetic data. Parameters of the simulated data were set as follows:

Gcycl_feature = 1-Normal Distribution, mu = 0.5, sigma = 0.1;

Gcycl_object = 1-Normal Distribution, mu = 0.9, sigma = 0.1;

Gsameord_feature = 1-Normal Distribution, mu = 0.9, sigma = 0.1;

Gsameord_object = 1-Normal Distribution, mu = 0.9, sigma = 0.1;

Gswap_nonswapped_object = 1-Normal Distribution, mu = 0.9, sigma = 0.1;

Gswap_nonswapped_feature = 1-Normal Distribution, mu = 0.6, sigma = 0.1;

Gswap_swapped_object = 1-Normal Distribution, mu = 0.9, sigma = 0.1;

Gswap_swapped_feature = 1-Normal Distribution, mu = 0.4, sigma = 0.1;

p_swap = 1-Normal Distribution, mu = 0.16, sigma = 0.02;

p_cycl_given_not_swap = 1-Normal Distribution, mu = 0.04, sigma = 0.01;

p_cycl = p_cycl_given_not_swap . (1-p_swap);*

prec_col = Normal Distribution, mu = 11, sigma = 0.01

prec_loc = Normal Distribution, mu = 15, sigma = 0.01

In terms of probabilities, normal distributions were truncated to fall within the range of 0 to 1. A total of 5000 trials for one participant were simulated this way and fed into the

model. The graph (**Fig. 4.14**) suggests a good approximation of the model to the underlying data.

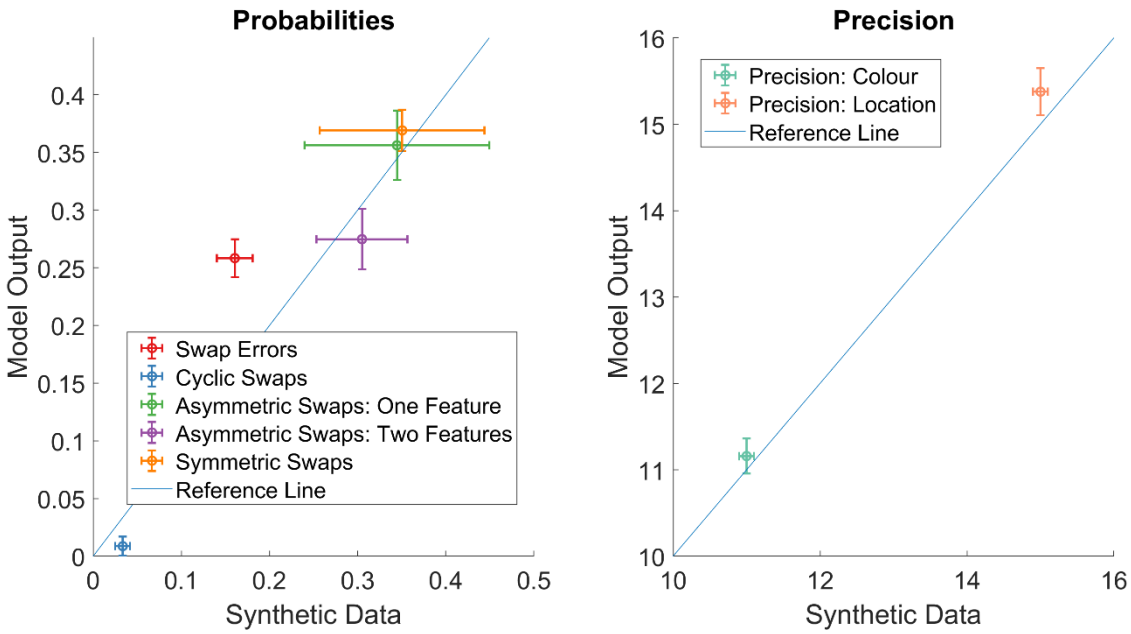


Figure 4.13 | Parameter recovery of synthetic data for the variables of interest. The approximation shows a reasonably close fit between simulated and recovered data.

4.5 Discussion

In both experiments, we asked participants to reproduce colours and locations of three dots with or without a cue. In the latter conditions, participants were required to reproduce all features on all dimensions of the memory array. Thus, researchers can directly assess within object binding between features and examine the fate of every single remembered feature. Yet, such privilege of cueing without a cue comes at the cost of sharing participants' uncertainty about which response refers to what target. To overcome this natural effect of such task and in order to allow to investigate effects of feature binding through-out the whole array, we introduce a new Bayesian hierarchical mixture model of free full report errors.

The main purpose of the model is to divide swap errors into symmetrical versus asymmetrical swaps where the former are swaps in which two features of two different objects are independently exchanged for one another. The latter, however, suggests that one object's feature takes another object's feature in the representation of the array, but the exchange is not symmetrical. An effect that is caused by forgetting on one feature or both features of one object of the potential swap. Unlike Bays et al. (2011), who rarely saw correlated feature guesses (= object guess), within our dataset, they account for almost 50% of the asymmetric swaps. Yet, swaps are generally rare in free recall conditions and cyclic swaps almost do not happen at all.

Testing participants either by having them reproduce the colour or the location first revealed that the parameters at probe generally worsened when participants were to first reproduce the colour. Thus, the experiments provide further evidence for an asymmetric or privileged binding of locations in objects as suggested previously (Heuer et al., 2016; Heuer & Schubö, 2016; Schneegans & Bays, 2017). The direct comparison between the first and second experiment further suggests that Swap Errors occurred significantly more often in the sequential experiment while Cyclic swaps were reduced. In the simultaneous experiment where all items are presented on the same screen, symmetric swaps, in which information is symmetrically exchanged, occur more often. Especially the precision for colour was increased in the sequential experiment. The fact that some model parameters improve, and some worsen in sequential over simultaneous experiments and vice versa sheds new light on the ambiguous literature on difference between sequential and simultaneous presentation. Only a free full report experiment will be able to fully reveal such differences.

The model and unique way of testing allow to systematically assess questions pointed out by previous research by directly assessing binding between features and probing for all objects. This will allow researchers to assess the effects of different manipulations, such as delay or set size, on feature binding. For this purpose, we made our model, together with instructions, available for researchers on OSF and encourage its use.

Our way of testing short-term memory allows for further conclusions about retrieval. Notably, reaction times are increased for the very first feature that was

reproduced which was true for cued and uncued conditions. Any of the following features were reproduced almost instantaneously, suggesting there was no additional time cost in retrieving features or objects after the first one. Furthermore, the second experiment shows that participants clearly preferred to reproduce sequences in the same order in which they had seen them. Rarely, they started with the object they had seen first and continued with the last-seen item but only occasionally did they reproduce objects in any other order. This might support evidence for information storage and replay in the order of presentation as suggested in chaining models (Osth & Dennis, 2015; Solway et al., 2012). Together with the reaction time, the results suggest that participants only have an initial reaction time cost, after which they follow a pre-composed plan of reporting features.

Absolute error of recall revealed two main results. Unsurprisingly, participants reproduced the best remembered item first. In addition, over both experiments, participants performed worse when reproducing the memory array with the help of a cue.

Several models have suggested a pattern completion account of short-term memory retrieval (Manohar et al., 2019; Tabi et al., 2019) according to which the probe's feature, i.e. its colour or location, triggers retrieval of the feature to be reported. Hence, one might think the cue could in fact be a boost through pattern completion, potentially leading to faster and more accurate responses on the dimension to be reproduced. However, neither the reaction time, nor the distance

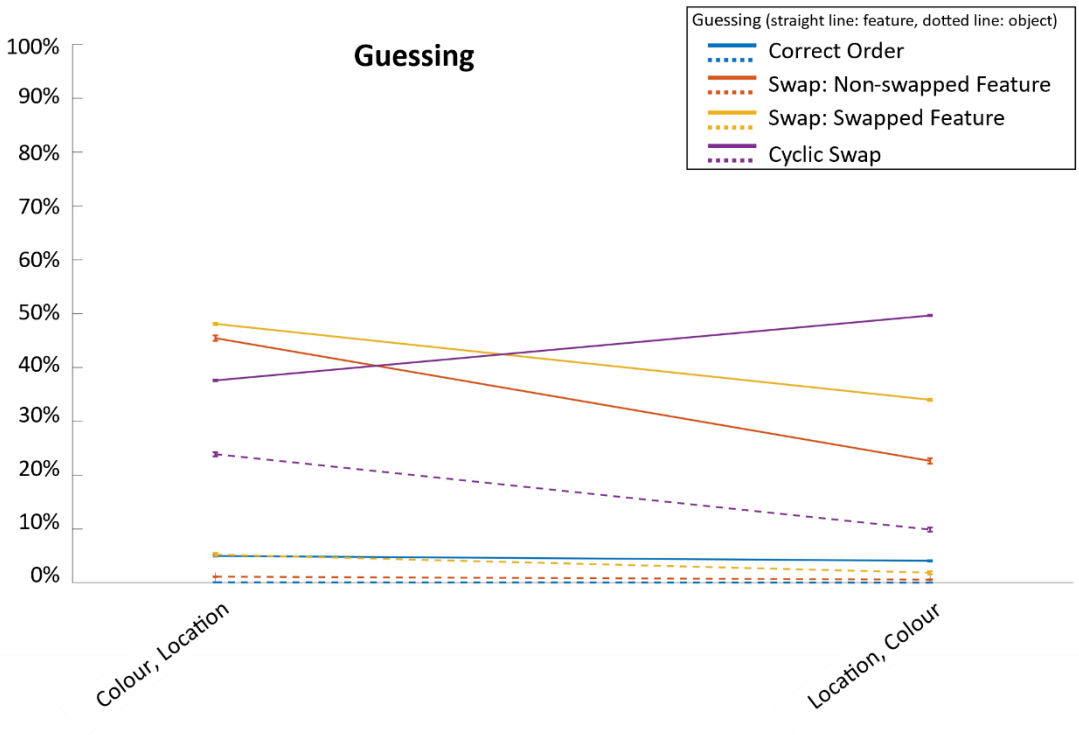
between targets and responses, the absolute error, showed any benefit for pattern completion through presentation of a probe. It was, on the contrary, in the free recall conditions that participants reported colour and location most precisely. Crucially, this cannot be accounted for by the amount of information or the order in which participants reproduced stimuli. I.e., in the cued recall conditions, participants would reproduce less information from memory and in all conditions, they were able to reproduce objects in whatever order they pleased, and timings were comparable.

One possible explanation for this could be a true perceptual interference caused by the presence of the cues on the screen (i.e. the presence of coloured squares or grey dots), thus feature-level competition through visual probing could lead to lower performance.

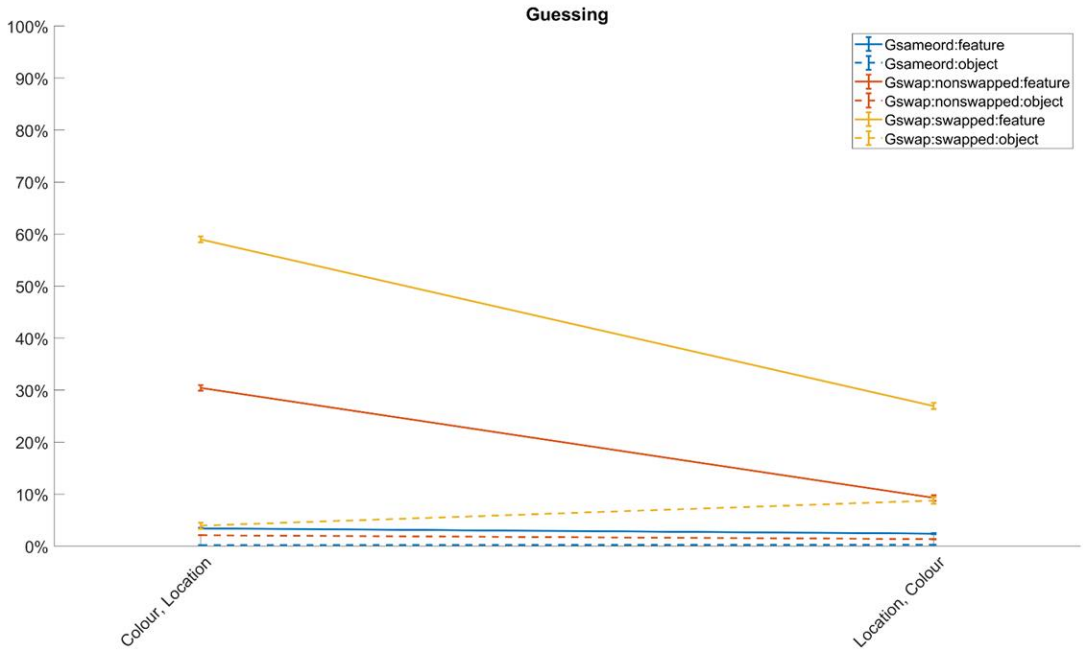
Based on the data, our Bayesian hierarchical model can explain these effects by a large increase of swap errors in cue conditions. However, the presented model has not primarily been developed to assess cued recall conditions and will assume participants' precision on the cued dimension to be infinite which could partly explain an artificial increase of misbinding in the cued condition.

In conclusion, the model presented here provides a new and unique perspective on retrieval, as well as feature binding over the whole memory array and thus opens a new category for research to be conducted which, by providing this model, we encourage researchers to follow up on.

4.6 Supplementary Materials



Supplementary Figure 4.1 | Independent guessing probabilities for experiment 1. Feature and object guessing are plotted given both swap types (Swap and Cyclic Swap) and for trials without a swap (Correct Order). Within swap trials, guessing was assumed to be different for the swapped and non-swapped items. Guessing for the whole object (dotted lines) as well as for the individual features (straight lines) were also differentiated. In general, guessing on the whole object occurred much less than for the individual feature. When features were swapped, people were generally more likely to guess compared to when they did not do a swap error.



Supplementary Figure 4.2 | Independent guessing probabilities for experiment 2. Feature and object guessing are plotted given both swap types (Swap and Cyyclic Swap) and for trials without a swap (Correct Order). The trends of the second experiment are in line with the results of the first experiment.

Supplementary Table 4.1: Post-hoc tests on the effect of the probe and reproduction modality on the unsigned error in Experiment 1

		Prior Odds	Posterior Odds	$BF_{10, U}$	error %
Location First (Location Response)	Location First (Colour Response)	0.260	1.059e +6	4.075e +6	3.620e -13
	Colour First (Location Response)	0.260	1688.377	6495.729	7.171e -10
	Colour First (Colour Response)	0.260	659391.925	2.537e +6	7.170e -13
	Colour Given (Location Response)	0.260	2.919e +12	1.123e +13	4.836e -19
	Location Given (Colour Response)	0.260	3.103e +6	1.194e +7	6.558e -14
Location First (Colour Response)	Colour First (Location Response)	0.260	419.413	1613.619	2.444e -9
	Colour First (Colour Response)	0.260	0.070	0.268	1.987e -5
	Colour Given (Location Response)	0.260	0.350	1.345	0.007
	Location Given (Colour Response)	0.260	32.195	123.865	9.927e -9
Colour First (Location Response)	Colour First (Colour Response)	0.260	1801.312	6930.226	6.748e -10
	Colour Given (Location Response)	0.260	7.481e +9	2.878e +10	7.289e -14
	Location Given (Colour Response)	0.260	11970.017	46052.511	9.781e -11
Colour First (Colour Response)	Colour Given (Location Response)	0.260	0.110	0.422	1.175e -5

Supplementary Table 4.1: Post-hoc tests on the effect of the probe and reproduction modality on the unsigned error in Experiment 1

		Prior Odds	Posterior Odds	BF $_{10, U}$	error %
	Location Given (Colour Response)	0.260	5.675	21.834	5.989e -9
Colour Given (Location Response)	Location Given (Colour Response)	0.260	0.071	0.274	1.935e -5

Note. The posterior odds have been corrected for multiple testing by fixing to 0.5 the prior probability that the null hypothesis holds across all comparisons (Westfall, Johnson, & Utts, 1997). Individual comparisons are based on the default t-test with a Cauchy (0, r = 1/sqrt(2)) prior. The "U" in the Bayes factor denotes that it is uncorrected.

Supplementary Table 4.2: Post-hoc tests on the effect of the probe and reproduction modality on the unsigned error in Experiment 2

		Prior Odds	PosteriorOdds	$BF_{10, U}$	error %
Location First (Location Response)	Location First (Colour Response)	0.260	178944.252	688456.174	9.638e -13
	Colour First (Location Response)	0.260	42.502	163.520	2.431e -8
	Colour First (Colour Response)	0.260	5.183e +7	1.994e +8	6.047e -12
	Colour Given (Location Response)	0.260	5.266e +11	2.026e +12	5.212e -18
	Location Given (Colour Response)	0.260	1.165e +11	4.484e +11	1.343e -17
Location First (Colour Response)	Colour First (Location Response)	0.260	22.409	86.214	3.849e -8
	Colour First (Colour Response)	0.260	1.223	4.706	1.100e -8
	Colour Given (Location Response)	0.260	10218.740	39314.783	7.361e -11
	Location Given (Colour Response)	0.260	10.219	39.314	5.988e -8
Colour First (Location Response)	Colour First (Colour Response)	0.260	7958.854	30620.275	1.015e -10
	Colour Given (Location Response)	0.260	3.260e +8	1.254e +9	2.416e -12
	Location Given (Colour Response)	0.260	4.368e +6	1.681e +7	2.556e -14

Supplementary Table 4.2: Post-hoc tests on the effect of the probe and reproduction modality on the unsigned error in Experiment 2

		Prior Odds	Posterior Odds	$BF_{10, U}$	error %
Colour First (Colour Response)	Colour Given (Location Response)	0.260	9.078	34.928	6.301e -8
	Location Given (Colour Response)	0.260	0.048	0.186	1.730e -5
Colour Given (Location Response)	Location Given (Colour Response)	0.260	8.654	33.296	6.423e -8

Note. The posterior odds have been corrected for multiple testing by fixing to 0.5 the prior probability that the null hypothesis holds across all comparisons (Westfall, Johnson,& Utts, 1997). Individual comparisons are based on the default t-test with a Cauchy (0, r

= 1/sqrt(2)) prior. The "U" in the Bayes factor denotes that it is uncorrected.

Supplementary Table 4.3: Post Hoc Comparisons of Reproduction Order for Experiment 2

		Prior Odds	Posterior Odds	$BF_{10, U}$	error %
123	213	0.260	7.295e +68	2.807e +69	1.222e -72
	312	0.260	8.593e +63	3.306e +64	1.272e -67
	132	0.260	6.909e +57	2.658e +58	1.650e -61
	321	0.260	1.049e +68	4.037e +68	2.148e -71
	231	0.260	6.738e +67	2.592e +68	2.210e -71
213	312	0.260	0.115	0.443	1.538e -6
	132	0.260	4.069e +15	1.566e +16	3.745e -22
	321	0.260	0.029	0.111	1.118e -5
	231	0.260	0.042	0.162	5.061e -6
312	132	0.260	1.284e +12	4.941e +12	3.458e -19
	321	0.260	0.295	1.136	1.108e -6
	231	0.260	0.319	1.227	1.096e -6
132	321	0.260	2.461e +15	9.470e +15	5.699e -22
	231	0.260	7.232e +16	2.782e +17	2.946e -23
321	231	0.260	0.031	0.118	9.860e -6

Note. The posterior odds have been corrected for multiple testing by fixing to 0.5 the prior probability that the null hypothesis holds across all comparisons (Westfall, Johnson,& Utts, 1997). Individual comparisons are based on the default t-test with a Cauchy (0, r = 1/sqrt(2)) prior. The "U" in the Bayes factor denotes that it is uncorrected.

5. Cholinergic effects on the focus of attention

5.1 Abstract

The cholinergic deficit in Parkinson's disease dementia motivated the use of cholinesterase inhibitors in the past. Despite the widespread use of such drugs like rivastigmine, the mechanisms underlying its benefit in short-term memory are to be fully understood and the full potential of the use of cholinesterase inhibitors in disease to be unravelled. In this study, the effects of rivastigmine on short-term memory and stabilizing the focus of attention in particular are investigated using a rivastigmine withdrawal design. I tested 17 participants suffering from Parkinson's disease dementia on and off their regular dose of rivastigmine on a retro-cue task that required focusing attention on one of two presented items, a manipulation known to make some items more readily available for use than others. Though the results do not show rivastigmine to stabilize the focus of attention, they reveal that rivastigmine directly improves visuospatial short-term memory in general. Even though holding items in the focus of attention seems independent of levels of acetylcholine, acetylcholine may improve short-term memory performance via general attentional effects.

5.2 Introduction

Acetylcholine is a ubiquitous transmitter present in the central as well as peripheral nervous system. Its function in the vegetative nervous system and the motor end plate are well studied. I.e., it is well-known that acetylcholine is the

neurotransmitter of all preganglionic autonomic neurons, as well as the transmitter for postganglionic parasympathetic neurons. Moreover, acetylcholine is responsible for transmitting neuronal signals in postganglionic sympathetic neurons connected to sweat glands. Thus, acetylcholine is ubiquitous messenger in the human body and yet its role in the central nervous system is yet to be fully understood.

There have been several different hypotheses regarding the involvement of acetylcholine in, for example, learning and uncertainty (A. Yu & Dayan, 2002), motivation (Berke, 2018) and attention (Klinkenberg et al., 2011). Moreover, previous research suggests an important role of acetylcholine in memory. When volunteers were injected with hyoscine, a ACh-receptor antagonist, they performed significantly worse when asked to remember a word list during an interpolated scanning task of 64 seconds. They did, however, show no effects of interference of Hyoscin when asked to reproduce the word list right after presentation (Crow & Grove-White, 1973). Therefore, the authors concluded that a central absence of acetylcholine impairs people's long-term but not short-term memory.

Further evidence for an association between memory and acetylcholine in the central nervous system derives from animal studies. I.e., in common marmosets with artificially inflicted unilateral lesion of the basal nucleus of Meynert, a acetylcholine producing area of the frontal basal brain, Ridley and colleagues found choline acetyltransferase, the enzyme to produce acetylcholine, to show

significantly reduced activity of up to 50% in the frontal and temporal cortex (Ridley et al., 1986). If such lesion to the basal nucleus of Meynert was applied bilaterally, the animals were impaired in their new visual object discrimination learning as well as object discrimination before the lesion. However, when Scopolamine, an acetylcholine agonist was applied, the animals' performance significantly improved. Further research in Rhesus monkeys showed that learning deficits are particularly linked to cholinergic cell loss in the basal nucleus of Meynert but not to general tissue damage.

Degeneration of the basal nucleus of Meynert can not only occur due to external manipulation but is a common symptom in Parkinson's Disease patients with dementia (Gratwicke et al., 2015). A depletion of up to 80% in the basal nucleus of Meynert in Parkinson's disease has been reported in previous studies (A. King et al., 2015). Though such cell loss in the basal nucleus of Meynert has also been reported in Alzheimer's Disease, data suggest that it is more pronounced in Parkinson's Disease (Candy et al., 1983). Further, using positron emission tomography to measure in vivo cortical levels of Acetylcholinesterase, the enzyme decomposing acetylcholine in the synapse and thus an indirect marker of acetylcholine levels, Bohnen and colleagues (Bohnen et al., 2006) showed acetylcholine not only to be significantly decreased in Parkinson's Disease Dementia but acetylcholine levels to also be correlated with quantitative short-term memory tasks such as the digit span in which participants are to remember an increasing number of digits.

In particular, acetylcholine has been linked to directing attention in short-term memory and related to the prefrontal and parietal cortex (see Klinkenberg et al., 2011 for a review on Acetylcholine in animals and humans). Physostigmine, a cholinesterase inhibitor which is known to increase acetylcholine in the synaptic cleft, improves selective attention and augmented activity in dorsolateral and medial prefrontal cortex (Bentley et al., 2004). Bentley and colleagues (Bentley et al., 2008) also linked the effects of physostigmine in AD patients to an improvement of their ability to direct attention. Patients did not only improve behaviourally but normally attenuated BOLD signals in the precuneus and posterior parahippocampal cortex increased after administration of physostigmine.

A cognitive system particularly entwined with attention is working memory. It has been hypothesized that working memory is also modulated by virtue of cholinergic effects on attentional aspects of tasks (Sarter et al., 2003) but research on the effects of acetylcholine on short-term memory remain relatively sparse: Items prioritised in working memory are referred to as being in the Focus of Attention (Lewis-Peacock et al., 2012; Oberauer & Lin, 2017; Souza & Oberauer, 2016). The item that is in the focus of attention is recalled faster and more accurately compared to other retained items. Other items outside the focus of attention are still retrievable but in a different representational state, encoded in activity silent synaptic traces (Manohar et al., 2019). The effects of acetylcholine in this equation are yet to be understood. In order to manipulate items in the focus of attention,

Zokaei and colleagues (Zokaei, Manohar, et al., 2014) used the incidental retro-cue task described in detail in chapter 3.

In this study, we aim to investigate the effects of Rivastigmine on the focus of attention in visuospatial short-term memory. For this purpose, the second experiment of the third chapter of this thesis was used. Participants were to remember the colour and orientation of an arrow as well as the screen half it was presented on. A first incidental retro-cue task asked them to report which screen size the arrow was presented on followed by an orientation task in which one arrow's orientation was to be reproduced. Given the retro-cue and the final orientation task would only ask for details of the same item in 50% of cases and correctly solving the retro-cue task would not give an advantage for solving the orientation task, the retro-cue task is incidental. In the third chapter, the incidental retro-cue was shown to yield benefits in retrieval in line with shifting attention, which makes this manipulation ideal for testing our hypothesis that Rivastigmine will improve precision for items stored in the focus of attention in particular.

5.3 Methods

Participants

17 patients suffering from Parkinson's Disease Dementia were recruited. Demographics for these are available in Tables 5.1-5.2.

Table 5.1 | Patients' mean ACE scores ON and OFF medication

	ACE: Attention	ACE: Memory	ACE: Fluency	ACE: Language	ACE: Visuospatial	ACE: Total
ON medication	15.44 (SD = 2, MIN = 11, MAX = 18)	20.94 (SD = 3.28, MIN = 15, MAX = 25)	9.44 (SD = 2.48, MIN = 6, MAX = 14)	24.69 (SD = 1.78, MIN = 19, MAX = 26)	14.31 (SD = 2.02, MIN = 9, MAX = 16)	84.77 (SD = 6.41, MIN = 75, MAX = 97)
OFF medication	15.77 (SD = 2.11, MIN = 11, MAX = 18	19.29 (SD = 4.17, MIN = 10, MAX = 26)	8.71 (SD = 3.12, MIN = 3, MAX = 14)	24.94 (SD = 1.98, MIN = 22, MAX = 26)	13.88 (SD = 2.09, MIN = 9, MAX = 16)	82.59 (SD = 6.22, MIN = 71, MAX = 95)

Table 5.2: Patients' mean Age, UPDRS scores and Levodopa-Equivalent Dosage

Age	UPDRS I	UPDRS II	UPDRS III	UPDRS IV	UPDRS Total	Hoehn-Yahr Staging	Levodopa-Equivalent Dosage
68.06 (SD = 8.61, MIN = 58, MAX = 88)	13 (SD = 8.70, MIN = 0, MAX= 35)	15.24 (SD = 12.47, MIN = 0, MAX = 40)	41.53 (SD= 22.60, MIN = 3, MAX = 78)	0 (SD = 0, MIN = 0, MAX = 0)	66.65 (SD = 35.35, MIN = 3, MAX = 134)	2.63 (SD = 1.09, MIN = 2, MAX= 5)	333.63 (SD = 344.69, MIN = 0, MAX = 900)

Procedure

The participants were asked to do a variation of the second experiment of chapter 3. Participants were presented with two arrows the orientations of which they were to remember for a period of 1000ms (**Fig. 5.1**). After a delay of 500ms, the patients were presented with the name of the colour of one of the two arrows (incidental retro-cue). Here, they were to either click the left or the right arrow key indicating whether the arrow of the shown colour was presented on the left or the right side of the screen. Their choice was followed by another delay of 1000ms or 3000ms after which the volunteers were to report the orientation of one of the initially presented two arrows. The target arrow was indicated by a coloured arrow probe the orientation of which started at a random angle. Using the mouse, participants were able to change the orientation of this arrow probe. Once the mouse cursor was moved, the arrow would point toward it so the angle could be arranged according to the target angle. There was a 50% chance that the colour presented in the incidental retro-cue was identical to the colour presented in the orientation probe (valid retro-cue). In total, there were four conditions (retro-cue validity x delay).

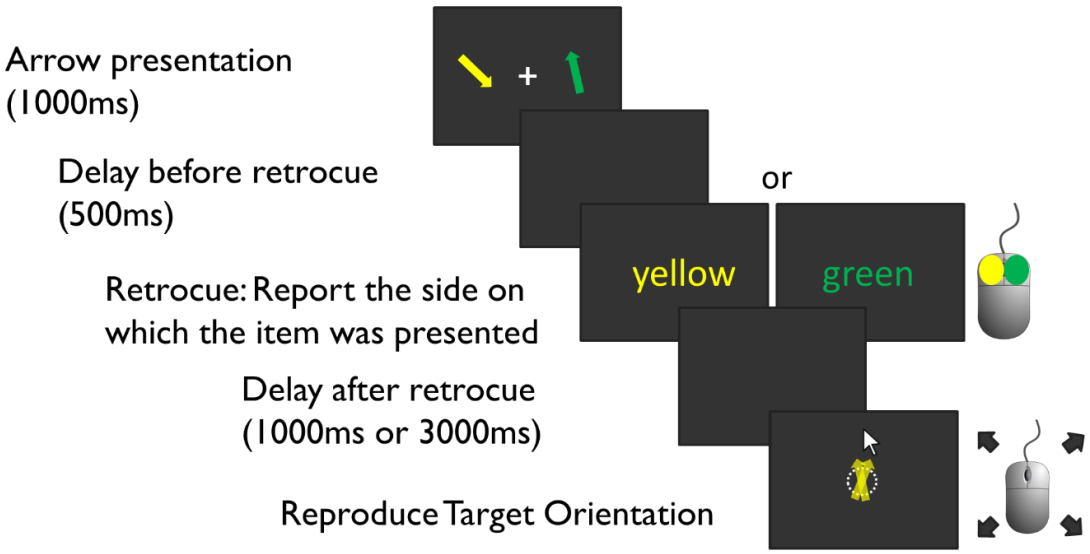


Figure 5.1 | Experiment Schematic. Volunteers were presented with two arrows for a period of 1000ms. After a short delay of 500ms, they were to report the screen side one of the two arrows was presented on (incidental retro-cue). Following another delay of either 1000ms or 3000ms, participants were asked to reproduce the orientation of one of the arrows indicated by the probe's colour. In half of the trials, the probe and retro-cue colour were identical (valid retro-cue).

A total of 252 trials per session (ON and OFF Rivastigmine) were to be performed. 7 participants performed all 252 trials in both sessions and one participant performed 400 trials in their ON session and 252 trials in their OFF session due to a mistake during data collection when the task was set up for them. On average and excluding the participant that accidentally performed 652 trials in total, 226.56 trials (SD = 45.32, MIN = 127, MAX = 252) were performed in the ON and 189.81 (SD = 73.02, MIN = 57, MAX = 252) trials were performed in the OFF session. All participants were put on Rivastigmine within the last six months. Three started this medication in the process of the study presented here.

Another three volunteers had a transdermal Rivastigmine patch applied to their skin. Those that did not, did their last dosage of Rivastigmine on average 1.98 hours before the start of their ON session (SD = 0.81, MIN = 0.5, MAX = 3.5). At the beginning of their OFF session, volunteers were on average 23.18 hours abstinent from Rivastigmine (SD = 3.28, MIN = 17, MAX = 27).

Besides the fact that only those trials were included in which participants correctly identified the screen half the arrow was presented on (retro-cue task), there was another exclusion criterion: For each participant, the mean reaction time and standard deviation was calculated. Only those trials in which the individual took less than the mean plus twice the standard deviation were included for further analysis. Based on this, an average of 2.30% (SD = 1.12%) of trials were excluded per participant.

5.4 Results

There was evidence for participants performing significantly more trials of the task in the ON compared to the OFF condition (t = 2.25, p = 0.040). The proportion of trials in which participants correctly solved the retro-cue task significantly significantly increased from 77.1% (SD = 19.4%, MIN = 45.2%, MAX = 99.6%) OFF medication to 87.8% (SD = 16.8%, MIN = 51.6%, MAX = 99.5%) ON medication (t = 2.62, p = 0.018). Despite these significant differences in the short-term memory task, there was no significant difference in Total ACE scores between sessions (t = 1.48, p = 0.158). This was also neither the case for the difference in the Memory subscale of the ACE (t = 1.95, p = 0.070) but not in any of the other subscales

(Attention: t = 0.95, p = 0.359, Fluency: t = 0.82, p = 0.427, Language: t = 0.42, p = 0.682, Visuospatial: t = 1.12, p = 0.281).

A Repeated Measures ANOVA of *medication x delay x retro-cue validity* in the absolute error (**Fig. 5.2**) showed evidence for main effects of Medication (F(1,16) = 5.30, p = 0.035, η_p^2 = 0.249) and retro-cue validity (F(1,16) = 6.53, p = 0.021, η_p^2 = 0.290) but for none of the other factors or interactions (**Supplementary Table 5.1**), suggesting that Rivastigmine increased short-term memory performance in general but did not stabilize the focus of attention in particular. Reproducing results of the second chapter, a valid retro-cue did again improve performance.

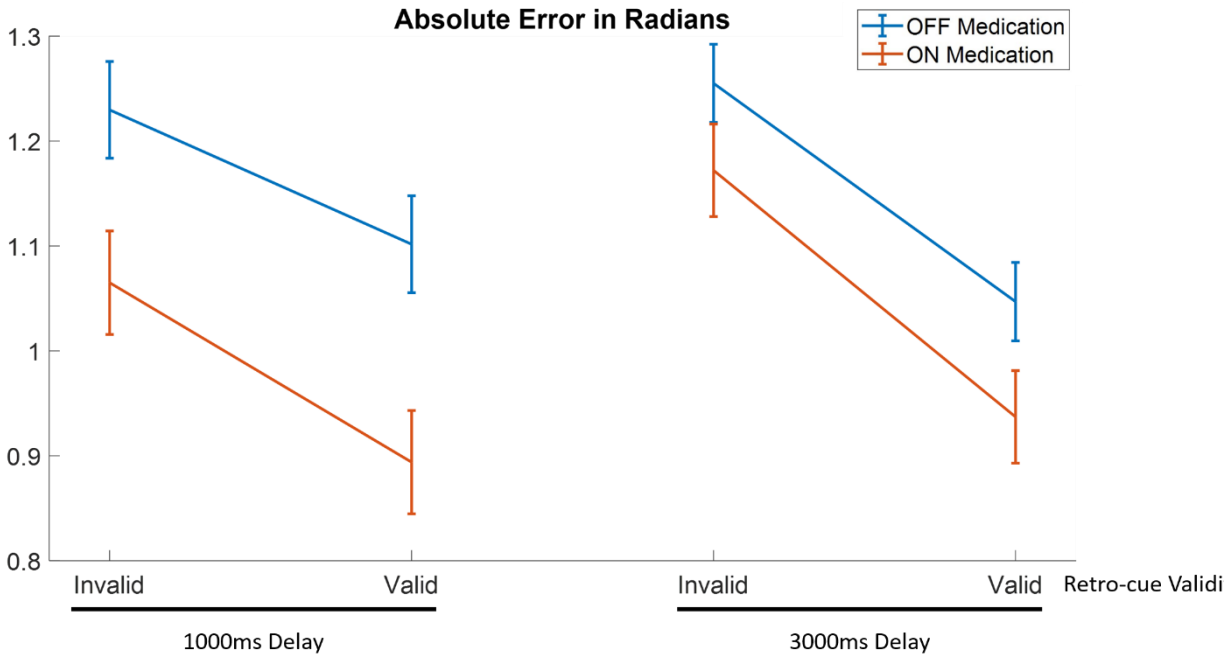


Figure 5.2 | Absolute Error in Radians. There were main effects of Medication and Retro-cue Validity, suggesting that the presentation of a valid retro-cue and administration of Rivastigmine decrease error in patients.

When the same 2x2x2-ANOVA was performed for the reaction times (**Fig. 5.3**), none of the main effects or interactions were significant (**Supplementary Table 5.2**).

The mixture model of error sources (**Fig. 5.4-5.5**) showed that misbinding, guessing and the concentration parameter were not affected by any of the main effects or interactions (**Supplementary Tables 5.3-5.5**).

In summary, none of the measures showed the expected interaction of Rivastigmine and Retro-cue which would have suggested that Rivastigmine would stabilize items held in the focus of attention. Instead, the study showed that the ability to prioritise items remains intact in Parkinson's disease dementia patients and significantly reduces the angular error. Moreover, we were able to provide evidence that Rivastigmine significantly decreases the absolute error despite the fact that Rivastigmine largely leaves overall cognition as measured by the ACE untouched.

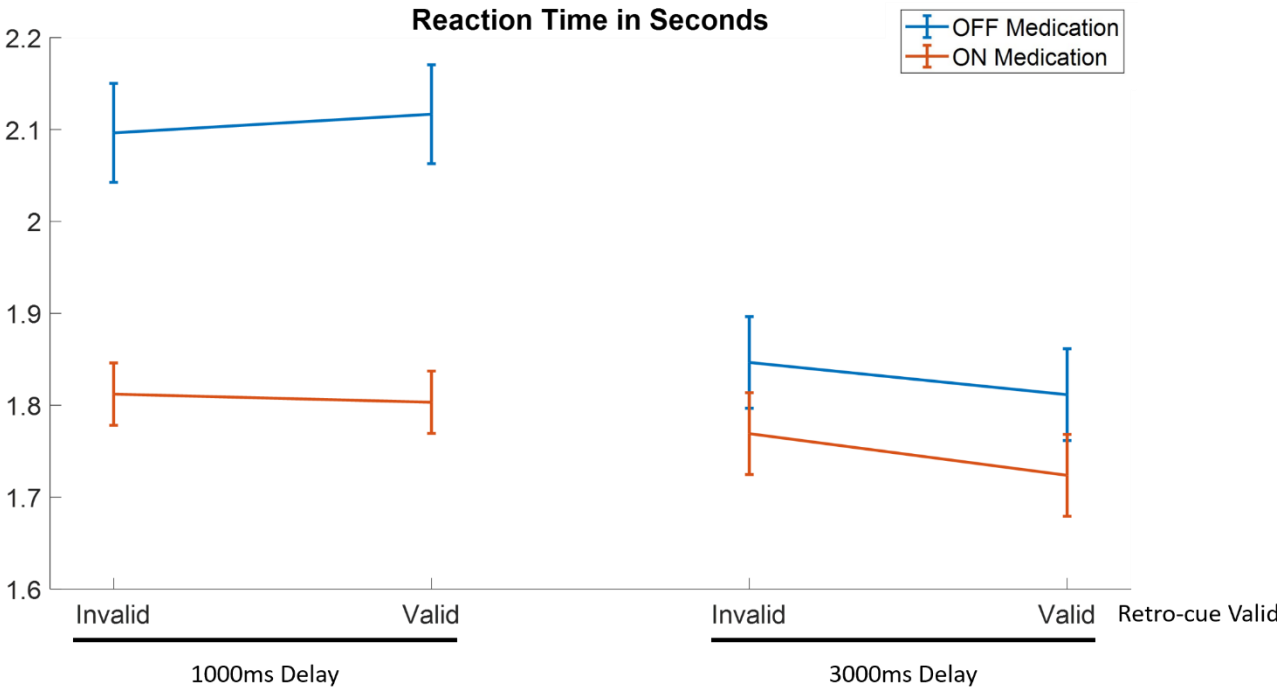


Figure 5.3 | Reaction Time in Seconds. There were no significant main effects or interactions in the reaction times, yet, visual inspection of the graph shows that reaction time was more noisy when participants were OFF their Rivastigmine.

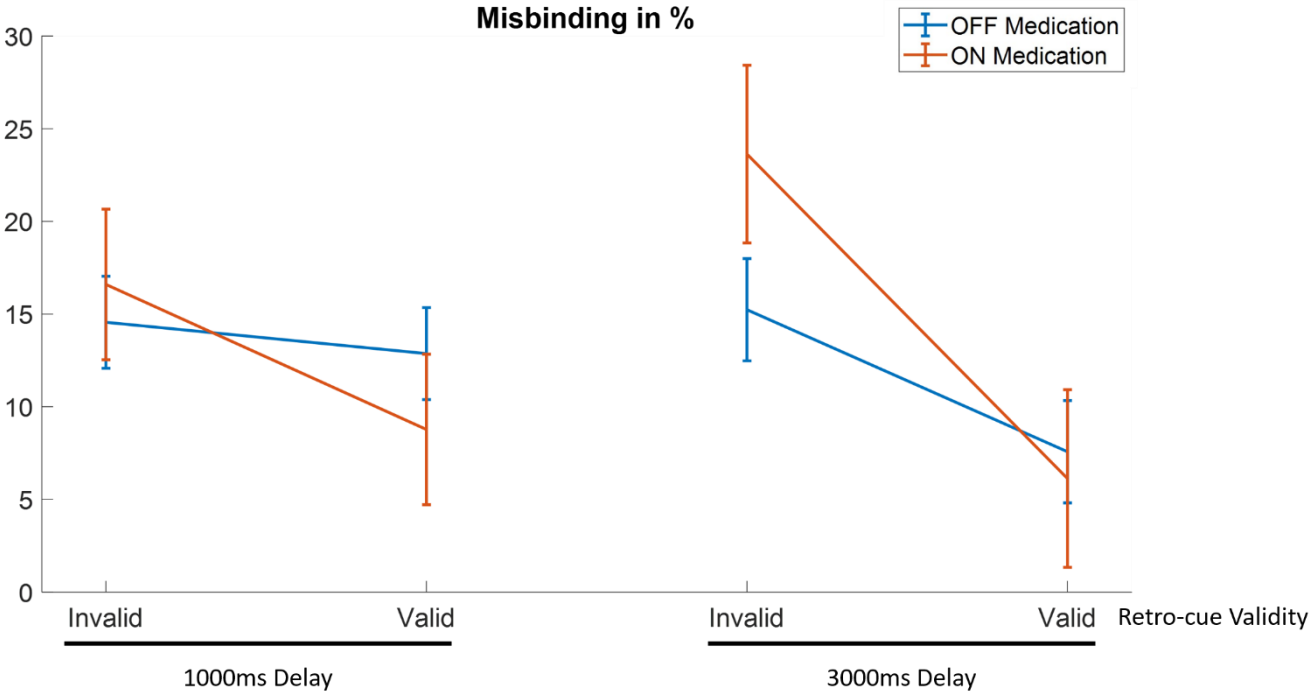


Figure 5.4 | Misbinding. None of the manipulations showed a significant effect on misbinding.

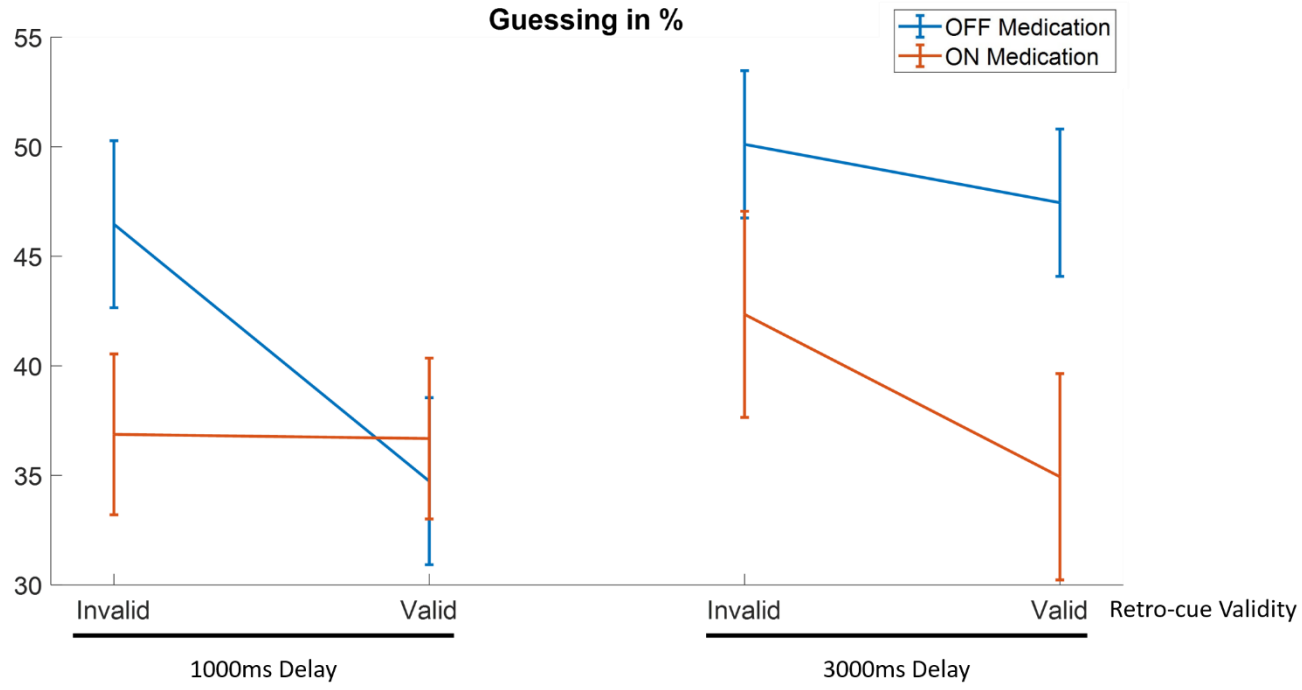


Figure 5.5 | Guessing. None of the manipulations showed a significant effect on guessing.

5.5 Discussion

In this study, we investigated the effects of Rivastigmine on the focus of attention in visual short-term memory. 17 patients suffering from Parkinson's disease dementia were recruited and tested on a continuous short-term memory task on and off Rivastigmine medication. Their attention was manipulated using an incidental retro-cue task as previously introduced in the third chapter of this thesis. Though the retro-cue and Rivastigmine each improved participant's performance, there was no interaction of these two factors. Retro-cueing decreased the angular error.

The goal of this study was to assess whether attentional gains from rivastigmine would be reflected in a short-term memory task manipulating the FOA (Zokaei, Manohar, et al., 2014; Zokaei, Ning, et al., 2014). Thus, we had hypothesized that rivastigmine would improve shifting attention and would thus improve the effects of an incidental retro-cue. The lack of an interaction of retro-cueing and Rivastigmine, however, suggests that Rivastigmine did not directly impact on shifts of attention but rather improved short-term memory performance as reflected by a decrease of error across the Rivastigmine conditions.

Previous studies showed that the injection of Scopolamine into the hippocampus showed disruption at encoding but not at retrieval. It is therefore possible that a retro-cue which in particular requires retrieval of information will not benefit from a central effect of Rivastigmine. Here, moving information in and out of the focus of attention was independent of effects of acetylcholine. Given the fact that

previous studies showed local scopolamine injection into the hippocampus to improve the encoding of information into memory, it seems like the shown effects of reduced noisiness after rivastigmine medication could derive from generally increased levels of attention during encoding. The missing interaction of Rivastigmine and delay is pointing at the fact that Rivastigmine does not stabilise retention. But with this failure to associate cholinergic effects to retention, the question is if the effect can be associated to encoding and retrieval. Maybe a lack of acetylcholine leads to complete failure to encode an item or complete failure to retrieve the cue or the feature that is to be reported during the trial. The improved performance participants showed in the retro-cue task would be in line with this fact. I.e., here participants completed significantly more retro-cue trials when they were on Rivastigmine compared to when they were off the drug. Hence, maybe their encoding and/or retrieval of information might have been improved under the influence of acetylcholine. This is also the case for general performance as indicated by the Absolute Error in radians. And there are further mechanisms of drug that could be ruled out by this study: There was no effect of Rivastigmine on the overall precision suggesting that Rivastigmine did not impact on adjustment of the participant's mental image. Rivastigmine might rather reduce general fluctuation of attention in patients. I.e., when correct and incorrect retro-cue responses are plotted over trials, some participants show clear patterns of incorrect responses occurring in chunks when off medication (**Fig. 5.6**, Participants 1, 6, 9 and 11) while others show a general pattern of such fluctuations no matter the medication (**Fig. 5.6**, Participants 14 and 16). So Rivastigmine might reduce attentional fluctuation in some patients.

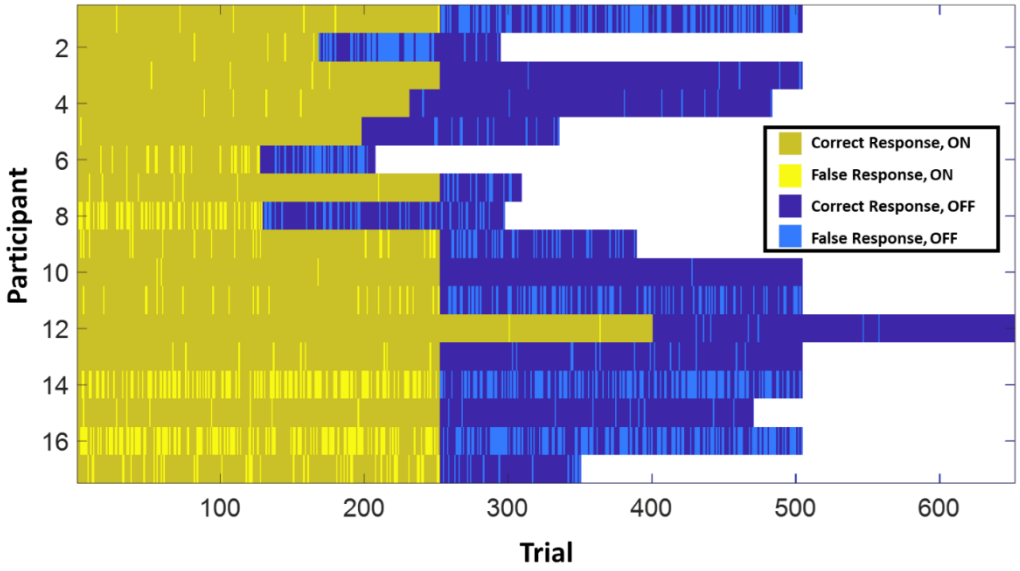


Figure 5.6 | Retro-cue responses plotted over trials on and off Rivastigmine for each participant. Some participants seem to express more erroneous *chunks* off medication (i.e., participants 1, 6, 9 and 11).

There is, however, a caveat to the results. All participants involved in the study were still on their regular dopaminergic medication for treatment of their motor results associated with Parkinson's disease. I.e., Calabresi and colleagues (Calabresi et al., 2006) suggest that cognitive dysfunction in Parkinson's disease is linked to dopamine-acetylcholine synaptic balance. In future studies, the interaction of the two transmitters on the focus of attention should be further explored, especially when they are used over longer periods of time. This is especially because Calabresi et al. (2006) suggest that the interaction of both acetylcholine and dopamine is involved in the maintenance of long-lasting striatal and cortical plasticity of synapses. Further, we hypothesized that the application of Rivastigmine will in particular fill in the cholinergic gap caused by the

degeneration of the nucleus basalis Meynert. The benefit of rivastigmine would thus rely on the degree to which the nucleus basalis Meynert is already degenerated. In summary, future studies should focus on long-term interactions of dopamine and acetylcholine and should consider the individual's benefit from acetylcholine respective to the degeneration of their nucleaus basalis Meynert. Another caveat is that this study included patients at different stages of disease. At later stages, increase of general cognitive impairment might play more of a role in being able to successfully do the task compared to earlier stages. Further, the brain might adapt to the drug in long-term use and withdrawal might be more severe in those individuals having been on medication for a while. Given the different times participants usually take their Rivastigmine, the withdrawal time together with half life will play an important role. Hence, future studies will have to take these drug specific aspects into account.

In conclusion, rivastigmine improves participants performance which could be explained by a general benefit for attention at encoding. Yet, there is no particular benefit from rivastigmine on the focus of attention as introduced by retro-cueing after the encoding phase in line with previous studies that see no benefit of acetylcholine on retrieval but rather on encoding.

5.6 Supplementary Materials

Supplementary Table 5.1: Repeated measure ANOVA of delay, medication and retro-cue validity on absolute angular error

Cases	Sum of Squares	df	Mean Square	F	p	η^2_p
Delay	0.031	1	0.031	1.395	0.255	0.080
Residuals	0.356	16	0.022			
Medication	0.679	1	0.679	5.296	0.035	0.249
Residuals	2.051	16	0.128			
Retro-cue Validity	1.171	1	1.171	6.526	0.021	0.290
Residuals	2.870	16	0.179			
Delay ✻ Medication	0.069	1	0.069	1.829	0.195	0.103
Residuals	0.600	16	0.038			
Delay ✻ Retro-cue Validity	0.044	1	0.044	2.385	0.142	0.130
Residuals	0.296	16	0.018			
Medication ✻ Retro-cue Validity	0.010	1	0.010	0.264	0.614	0.016
Residuals	0.629	16	0.039			
Delay ✻ Medication ✻ Retro-cue Validity	5.520e-4	1	5.520e-4	0.018	0.896	0.001
Residuals	0.499	16	0.031			

Note. Type III Sum of Squares

Between Subjects Effects

Cases	Sum of Squares	df	Mean Square	F	p
Residuals	27.124	16	1.695		

Note. Type III Sum of Squares

Supplementary Table 5.2: Repeated measure ANOVA of delay, medication and retro-cue validity on reaction times

Cases	Sum of Squares	df	Mean Square	F	p	η^2_p
Delay	0.975	1	0.975	4.510	0.050	0.220
Residuals	3.460	16	0.216			
Medication	1.236	1	1.236	1.154	0.299	0.067
Residuals	17.137	16	1.071			
Retro-cue Validity	0.010	1	0.010	0.071	0.793	0.004
Residuals	2.278	16	0.142			
Delay ✻ Medication	0.397	1	0.397	3.231	0.091	0.168
Residuals	1.967	16	0.123			
Delay ✻ Retro-cue Validity	0.018	1	0.018	0.445	0.514	0.027
Residuals	0.645	16	0.040			
Medication ✻ Retro-cue Validity	0.003	1	0.003	0.047	0.831	0.003
Residuals	1.128	16	0.070			
Delay ✻ Medication ✻ Retro-cue Validity	7.573e-4	1	7.573e-4	0.021	0.887	0.001
Residuals	0.583	16	0.036			

Note. Type III Sum of Squares

Between Subjects Effects

Cases	Sum of Squares	df	Mean Square	F	p
Residuals	117.490	16	7.343		

Note. Type III Sum of Squares

Supplementary Table 5.3: Repeated measure ANOVA of delay, medication and retro-cue validity on Misbinding

Cases	Sum of Squares	df	Mean Square	F	p	η^2_p
Delay	0.034	1	0.034	2.078	0.169	0.115
Residuals	0.265	16	0.017			
Medication	0.090	1	0.090	4.049	0.061	0.202
Residuals	0.356	16	0.022			
Retro-cue Validity	0.338	1	0.338	2.730	0.118	0.146
Residuals	1.983	16	0.124			
Delay ✻ Medication	0.009	1	0.009	0.609	0.447	0.037
Residuals	0.247	16	0.015			
Delay ✻ Retro-cue Validity	0.056	1	0.056	2.002	0.176	0.111
Residuals	0.446	16	0.028			
Medication ✻ Retro-cue Validity	0.061	1	0.061	2.906	0.108	0.154
Residuals	0.334	16	0.021			
Delay ✻ Medication ✻ Retro-cue Validity	0.031	1	0.031	1.406	0.253	0.081
Residuals	0.352	16	0.022			

Note. Type III Sum of Squares

Between Subjects Effects

Cases	Sum of Squares	df	Mean Square	F	p
Residuals	1.563	16	0.098		

Note. Type III Sum of Squares

Supplementary Table 5.4: Repeated measure ANOVA of delay, medication and retro-cue validity on Guessing

Cases	Sum of Squares	df	Mean Square	F	p	η^2_p
Delay	92343.458	1	92343.458	0.774	0.392	0.046
Residuals	1.908e+6	16	119247.545			
Medication	236.982	1	236.982	0.002	0.964	1.278e-4
Residuals	1.855e+6	16	115908.665			
Retro-cue Validty	17941.657	1	17941.657	0.118	0.735	0.007
Residuals	2.425e+6	16	151549.947			
Delay ✻ Medication	4216.450	1	4216.450	0.038	0.848	0.002
Residuals	1.774e+6	16	110888.283			
Delay ✻ Retro-cue Validty	10854.522	1	10854.522	0.119	0.734	0.007
Residuals	1.454e+6	16	90846.005			
Medication ✻ Retro-cue Validty	526298.589	1	526298.589	4.415	0.052	0.216
Residuals	1.907e+6	16	119209.469			
Delay ✻ Medication ✻ Retro-cue Validty	49918.116	1	49918.116	0.320	0.579	0.020
Residuals	2.495e+6	16	155950.109			

Note. Type III Sum of Squares

Between Subjects Effects

Cases	Sum of Squares	df	Mean Square	F	p
Residuals	2.244e+6	16	140240.438		

Note. Type III Sum of Squares

Supplementary Table 5.5: Repeated measure ANOVA of delay, medication and retro-cue validity on the concentration parameter

Cases	Sum of Squares	df	Mean Square	F	p	η^2_p
Delay	92343.458	1	92343.458	0.774	0.392	0.046
Residuals	1.908e+6	16	119247.545			
Medication	236.982	1	236.982	0.002	0.964	1.278e-4
Residuals	1.855e+6	16	115908.665			
Retro-cue Validty	17941.657	1	17941.657	0.118	0.735	0.007
Residuals	2.425e+6	16	151549.947			
Delay ✻ Medication	4216.450	1	4216.450	0.038	0.848	0.002
Residuals	1.774e+6	16	110888.283			
Delay ✻ Retro-cue Validty	10854.522	1	10854.522	0.119	0.734	0.007
Residuals	1.454e+6	16	90846.005			
Medication ✻ Retro-cue Validty	526298.589	1	526298.589	4.415	0.052	0.216
Residuals	1.907e+6	16	119209.469			
Delay ✻ Medication ✻ Retro-cue Validty	49918.116	1	49918.116	0.320	0.579	0.020
Residuals	2.495e+6	16	155950.109			

Note. Type III Sum of Squares

Between Subjects Effects

Cases	Sum of Squares	df	Mean Square	F	p
Residuals	2.244e+6	16	140240.438		

Note. Type III Sum of Squares

6. Gamified Short-term memory task

6.1 Abstract

Within our aging society, the number of people presenting with memory impairments increases constantly. Given the importance of finding the right diagnosis, new memory measures are needed in order to distinguish symptoms resulting from severe impairment such as in Alzheimer's disease versus transient deficits as shown in depressive episodes. However, most widely available memory tests are not able to detect subtle changes of memory performance as shown in prodromal stages of Alzheimer's disease like Mild Cognitive Impairment. Moreover, tests often require patients to attend a clinic and need to be conducted by trained personnel. Here, a new gamified memory test is presented that can be provided at a large scale and that does not require healthcare professionals to be with the patient. In this study, 131 participants of different age groups were tested on this new gamified memory measure that uses object-location binding as a marker of hippocampal function given the hippocampus is one of the first regions to be affected by Alzheimer's disease. Besides showing that binding is directly correlated with hippocampal volume, the study shows that the ability to bind information into objects remains largely unaffected by healthy aging.

6.2 Introduction

Demographic changes lead to an aging society and consecutively to an increase of patients presenting with memory deficits. Their origin can range from temporary causes such as in depression to more severe causes like clinical dementia. The number of people living with dementia in 2050 is projected to increase by one million each year ("2016 Alzheimer's disease facts and figures", 2016), and within the group of 50 million people suffering from dementia today, two thirds suffer from Alzheimer's dementia (Kumar et al., 2021). With such growing incidence, there is a need for a large-scale screening tool. The hope for such a tool, of course, is to also alter the trajectory of the disease through early treatment. Though treatment with cholinesterase inhibitors is known to slow down the progression of Alzheimer's disease for a short period of time (Sharma, 2019 for a review), there is no medication available to efficiently cure it once and for all. Diagnosing Alzheimer's disease earlier using a screening tool could enable treatment before substantial loss of brain tissue has happened.

Another aim of new screening tools should be an increased sensitivity towards earlier, pre-clinical stages of Alzheimer's disease. Mild Cognitive Impairment (MCI) is known to be a pre-stage of clinical Alzheimer's disease. 10% of these patients are known to convert to Alzheimer's disease within five years (Petersen et al., 1999). However, common methods used for clinical testing, such as the Addenbrooke's Cognitive Examination, often lack the level of sensitivity to detect

subtle cognitive changes shown in MCI. One approach to solve this dilemma is to assess brain regions that are first affected by the disease. The hippocampus is the region that is most vulnerable at early stages of Alzheimer's disease (Braak et al., 1993). This brain region is known to be involved in internal mapping of space and events in interaction with long-term memory (O'Keefe & Nadel, 1978) and in representing distances between objects in space (Howard et al., 2014; Morgan et al., 2011). Moreover, the hippocampus has previously been proposed to be involved in path integration, the ability to update one's position in an internal, representative map after movement (S. Kim et al., 2013; Philbeck et al., 2004; Worsley et al., 2001).

Based on this, Coughlan and colleagues (Coughlan et al., 2019) created a task assessing wayfinding and path integration at large scale. In their task, the authors present participants with a visual map they are to memorize. Besides a water landscape of changing difficulty, the map comprises of a Start and a Finish point the distance between which participants are asked to travel in the shortest possible way, directing a boat through the water (wayfinding). After reaching the Finish point, participants are asked to shoot a flare towards where they started directing the boat (path integration). They were able to show that individuals at a higher risk of developing Alzheimer's disease in the future due to a variation of their ApoE genotype, travelled further distances in the wayfinding task compared to individuals without a genetic risk.

Another method that has been shown to detect small changes in participants' ability to remember information over a short period of time is a delayed

reproduction task with a two-forced-choice task (2FC). Typically, participants are shown one or multiple objects that they are asked to remember for a period of a few seconds. After a delay, they are asked to select the object they remembered from a set of two (2FC) and to move it to its previous location (delayed reproduction). Previous studies have shown patients suffering from Alzheimer's disease to exhibit a certain type of error in such tasks. These people show greater levels of misbinding of the object identities and their respective locations compared to healthy age-matched controls (Liang et al., 2016). Meaning that these patients suffering from Alzheimer's disease were more likely to mislocalize correctly identified shapes to the location of other items concurrently held in memory. This source of error has as well been found in patients suffering from limbic encephalitis (Pertzov et al., 2013), an inflammatory disease to the hippocampus. Further, it has been proposed that misbinding is an early behavioural marker in AD (Liang et al., 2016), MCI (Toniolo et al., 2020) and in those at genetic risk of developing Alzheimer's disease in the future (Zokaei et al., 2017).

Both, wayfinding and path integration, the measure used by Coughlan and colleagues (2019), and misbinding have been linked to the hippocampus (wayfinding/path integration: O'keefe & Nadel, 1978; misbinding: Pertzov et al., 2013). The hippocampus itself is known to be one of the first regions to be affected by Alzheimer's disease (Liang et al., 2016), setting the spot light for those that seek to find a measure of early detection.

Given that such a behavioural marker comes at a lower cost than established neuroimaging techniques, and can be assessed in a portable format by non-clinical personnel outside of a clinic, there is a lot of potential for such a task. Here, we used a gamified version of the short-term memory test that would allow participants to conduct the task in their own homes on a portable tablet. This format will, in the future, allow to test large groups of people at very low cost.

In the current study, we compare results of a lab- versus gamified home-based assessment, compare performance in the gamified version according to age and see if misbinding can be linked to the hippocampus.

6.3 Methods

Participants

131 participants were recruited and split into three age groups (45 aged between 18 and 30 years, 30 aged between 30 and 50 and 56 aged above 50 years): The 56 participants aged over 50 years underwent the standard lab task and the gamified version of the task (66.51 years on average, SD = 7.85). Volunteers in this group received a Samsung Galaxy Tab S3 through the mail and were instructed to use the app via phone while the App *Anydesk* allowed the live screen to be seen by the researcher and also allowed direct intervention if necessary. 43 of these patients underwent a structural T1 MRI scan (mean age = 65.63; SD = 8.10). Moreover, participants were recruited online that did report to be neurologically normal and were eligible for one of the two age groups (18-30 years and 30-50 years). Both of these *online groups* were to use their own tablets at home and all groups were instructed to place the tablet at a viewing distance of about 60cm.

Task

Participants were presented with either one or three white constellations on a dark background for a period of one second per constellation (i.e., one or three seconds, **Fig. 6.1**). The constellations consisted of a random number of nodes and connections and subtended a visual angle of approximately 2.3 degrees. After a delay of one or four seconds, two constellations appeared above and below the

screen centre one of which was the target and the other one a never-seen foil. Participants were to select the target and to drag it to its remembered location. As soon as they tapped on one of the constellations, the other one disappeared and thus their Identification choice was confirmed. As soon as they released the chosen constellation, a *Done* button appeared at the screen centre and participants could confirm their Localisation choice. If recruits touched the constellation again, they could adjust their choice until they finally pressed the *Done* button. In some trials, participants were to do an unrelated task during the delay interval. Here, once the constellations disappeared, a telescope lens and a star of the same size as the constellations appeared in random locations. Volunteers were to drag the lens to the star. After they reached the star with the lens, another star would appear, and they were to drag the lens to this next star. This process continued for a total of four seconds after which the two-star constellations appeared in the screen centre for the participant to make their Localisation choice. Thus, in total there were six different conditions:

- Condition 1: One constellation, short empty delay
- Condition 2: One constellation, long empty delay
- Condition 3: Three constellations, short empty delay
- Condition 4: Three constellations, long empty delay
- Condition 5: One constellation, long filled delay (telescope task during maintenance interval)

  Condition 6: Three constellation, four seconds delay, long filled delay (telescope task during maintenance interval)

In this chapter, I will focus on the four unfilled delay conditions that are identical to the four conditions of the original lab task and will analyse the two filled delay conditions separately.

Trials were split into four blocks. In each of the first and second block, 10 trials each of conditions 1 and 3 were presented. In addition, 8 trials each of conditions 2 and 4 were included in each of the first two blocks. Each of the last two blocks consisted of 2 trials each of conditions 2 and 4 in addition to 10 trials each of conditions 5 and 6. Thus, there were a total of 20 trials per condition in the experiment.

The original lab-based task was like the gamified version. The main difference was that differently-coloured fractals were used instead of constellations and there was no telescope task during the delay, thus no conditions 5 and 6. In the lab-based task, participants were to perform 30 trials of conditions 1-4 that were distributed equally over all four trials. In both, the gamified and the lab-based task, volunteers were allowed to take breaks the duration of which they could determine themselves.

In chronological order, the task provided the following measures:

Reaction Time: The time in seconds taken to identify the target when participants are presented with target and foil.

Identification Accuracy: The proportion of trials per condition in which participants correctly identified the target.

Localization Performance: The distance between their localization response and the actual target location.

The source of error in Localisation performance was investigated based on the mixture model brought forward by Bays and colleagues (Bays et al., 2011). Possible sources underlying Localisation Error could derive from **Misbinding** or **Guessing**. If participants remembered the presented screen locations and appearances of the stimuli but reported the wrong location for a correctly selected target, this can be interpreted as a feature-object misbinding. If no information on the location was remembered whatsoever and the circle dragged to a random location, this was defined as a random guess (Fig. 4.3).

In detail, misbinding and guessing were calculated the following way:

For each trial, the distance between the response and i) the target location, ii) the closest non-target location and iii) a random trial's non-target location were compared with one another. If the target distance (i) was smallest, the response was classified as a target response. If the non-target distance (ii) was smallest, the response was classified as a misbinding. If the distance between response and a random trial's non-target was smallest, this was classified as guessing. The procedure was repeated 5000 times with a random trial's non-target for each of the trials. Thus, in each trial, target and non-target distance were compared to the distance between the target and *all* other trials' non-targets. In addition, imprecision was calculated as the distance between the response and the closest stimulus in the original encoding display.

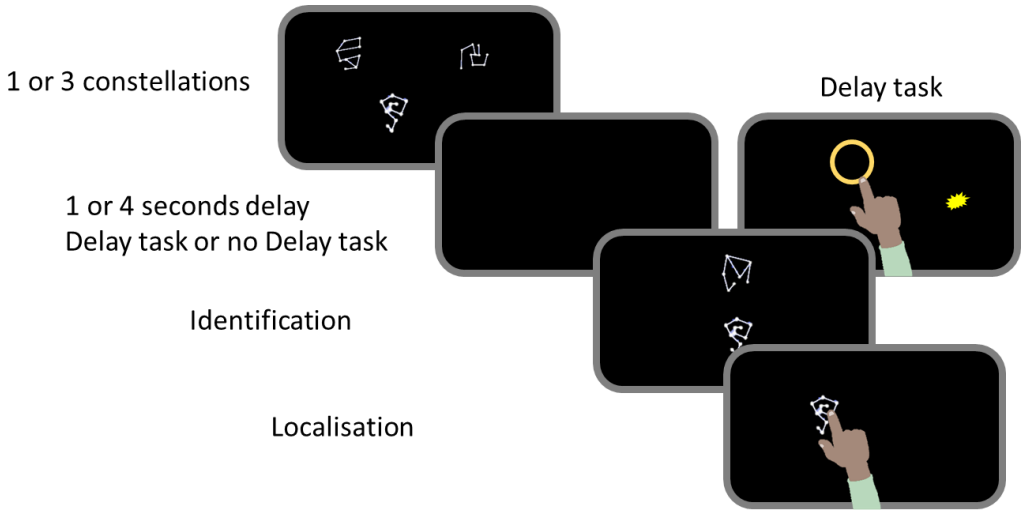


Figure 6.1 | Experiment Schematic. Participants were presented with either one or three star constellations. After a delay of 1 or 4 seconds, they were asked to identify the correct shape out of two presented on the screen and to drag it to the location they think they had seen it at. In half of the trials with a delay of 4 seconds, participants had to perform an unrelated delay task in which they dragged a telescope around the screen.

Here, a 3T Siemens Magnetom Verio syngo scanner was used to acquire T1-weighted volumetric images through a magnetisation prepared rapid gradient echo protocol (MPRAGE) in sagittal orientation (TR = 2000 msec, TE = 1.94 msec, TI = 880 msec, Flip angle = 8 degrees, FOV read = 256 mm, Voxel size = 1.0 x 1.0 x 1.0 mm). The same machine was also used to record T2-FLAIR images.

Hippocampal and hippocampal subfield volumes were calculated through the standard Freesurfer pipeline (cortical reconstruction and volumetric segmentation, documented and freely available for download online; http://surfer.nmr.mgh.harvard.edu/) and also corrected for age and total

intracranial volume. In addition, subfields of the hippocampus were decomposed using the software's subfield pipeline. These analyses used T1 and T2 image inputs.

6.4 Results

Lab-based task ("Fractals") in elderly controls

When the set size was increased from one to three items, volunteers identified less targets correctly (**Fig. 6.2**, F(1,55) = 142.85, p < 0.001, η_p^2 = 0.729), dragged the shape further away from the correct target location (F(1,55) = 292.56, p < 0.001, η_p^2 = 0.847) and took longer to make their initial response (F(1,55) = 322.33, p < 0.001, η_p^2 = 0.859).

An increase of the delay between the presentation of stimuli and the probe screen led to recruits moving the fractal further away from the target location (F(1,55) = 16.79, p < 0.001, η_p^2 = 0.241), there was evidence for them identifying less targets correctly (F(1,55) = 5.91, p = 0.018, η_p^2 = 0.100) and the delay also increased their reaction times (F(1,55) = 47.20, p < 0.001, η_p^2 = 0.471). The delay did not have an impact on Misbinding (t = 0.82, p = 0.055), Guessing (t = 1.11, p = 0.270) or Imprecision (t = 0.82, p = 0.417).

There was also evidence for an interaction of factors delay and set size in the Localisation error (F(1,55) = 5.45, p = 0.023, η_p^2 = 0.093) but this was neither the case in the Identification Accuracy (F(1,55) = 0.56, p = 0.458, η_p^2 = 0.010) nor the

Reaction Time (F(1,55) = 0.79, p = 0.378, η_p^2 = 0.015). Post-hoc t-tests showed that there was an effect of the delay in three items in the Localisation error (t = 4.55, p < 0.001) but much less so in one item (t = 1.25, p = 0.214).

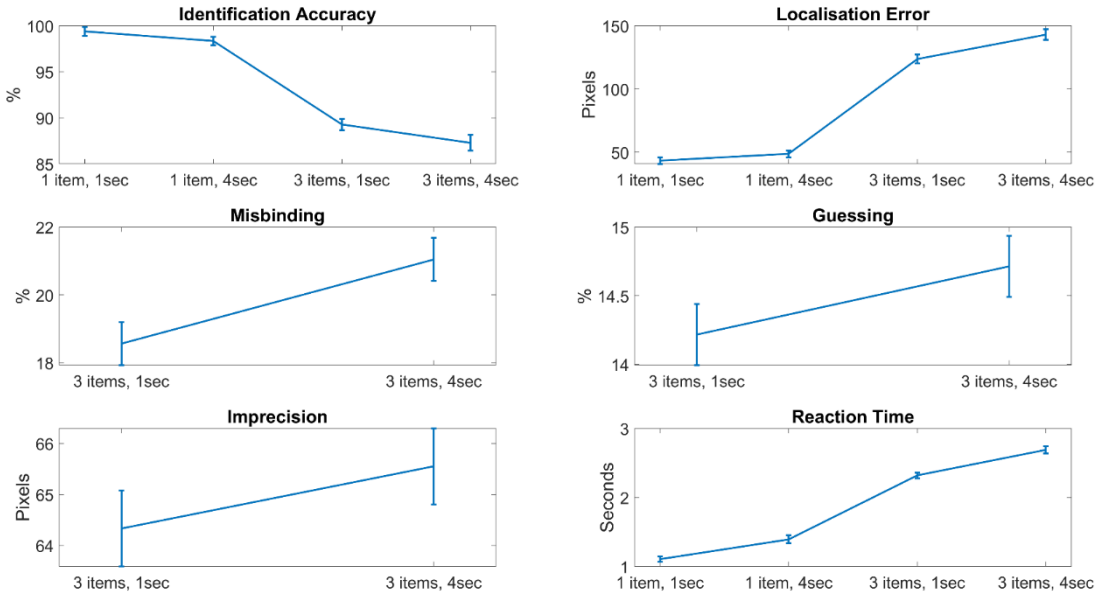


Figure 6.2 | Fractals results in elderly controls. An increase of the set size and a longer delay worsened the Identification Accuracy and increased the Localisation error. People were also performing generally slower.

Gamified Task ("Starry Night") in elderly controls

In the gamified task (**Fig. 6.3**), an increase of the set size from one to three items decreased the Identification Accuracy ($F(1,55) = 138.70$, $p < 0.001$, $\eta_p^2 = 0.716$), increased the Localisation error ($F(1,55) = 547.41$, $p < 0.001$, $\eta_p^2 = 0.909$) and the reaction time ($F(1,55) = 229.10$, $p < 0.001$, $\eta_p^2 = 0.806$). An increase of the delay from one to four seconds increased the Localisation Error ($F(1,55) = 4.86$, $p = 0.032$, $\eta_p^2 = 0.081$) but not the Reaction Times ($F(1,55) = 0.76$, $p = 0.386$, $\eta_p^2 = 0.014$) and the Identification Accuracy ($F(1,55) = 0.36$, $p = 0.553$, $\eta_p^2 = 0.006$). Looking at modelling parameters, the longer delay increased Guessing ($t = 2.85$, $p = 0.006$) and Imprecision ($t = 2.87$, $p = 0.006$) but left Misbinding unaffected ($t = 1.299$, $p = 0.203$). There was no interaction of factors delay and set size in the Identification Accuracy ($F(1,55) = 0.01$, $p = 0.909$, $\eta_p^2 = 0.000$), Localisation Performance ($F(1,55) = 1.46$, $p = 0.232$, $\eta_p^2 = 0.026$) and Reaction Times ($F(1,55) = 2.45$, $p = 0.124$, $\eta_p^2 = 0.043$).

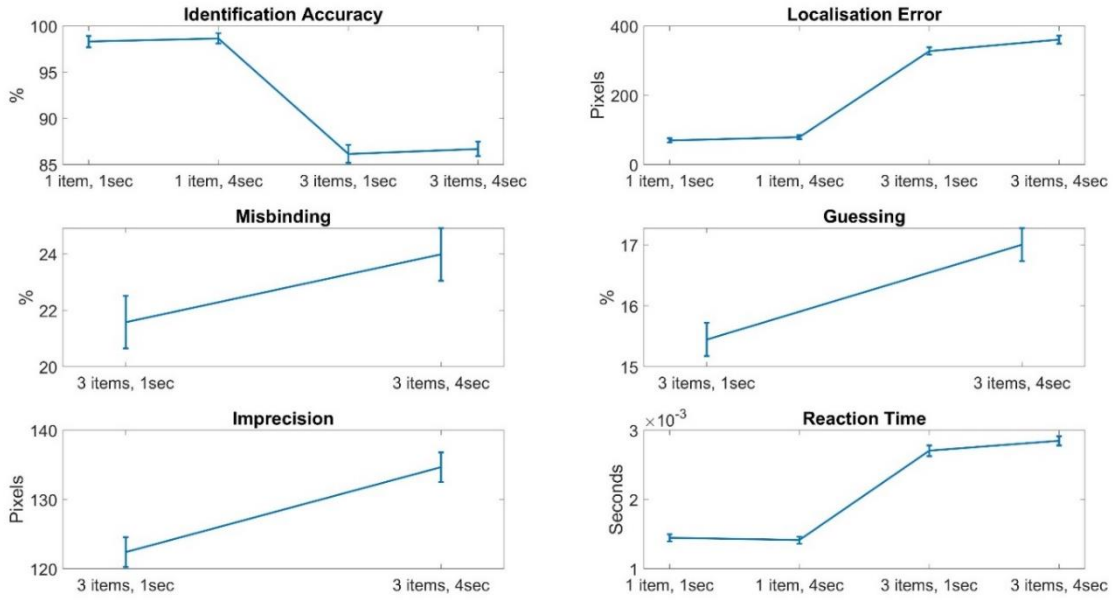


Figure 6.3 | Starry Night results for elderly controls. An increase of the set size worsened the Identification Accuracy and increased the Localisation error. People were also performing generally slower. Longer delays increased Guessing and Imprecision.

Comparing Misbinding in Fractals and Starry Night

Especially the correlation of misbinding as a marker for hippocampal decline was of interest in this study (**Fig. 6.4**). Therefore, we looked into the correlation between misbinding in conditions 3 and 4 between both tasks, the lab-based and the gamified version. There were significant correlations for both delays, 4 seconds ($r = 0.35$, $p = 0.011$) and 1 second ($r = 0.42$, $p = 0.001$) between both tasks, providing first evidence that a flexible home-used task can be administered to individuals without regular access to a neurology clinic or for large-scale testing. The caveat of this study, however, is that future studies should include at least 60 participants performing both tasks which should be conducted without too much time passing between the first and second measurement. Here, participants had performed the lab task up to one year before they did the task at home. This measure can therefore just be a first approximation. For a valid comparison, values of $r > 0.7$ are required in the future.

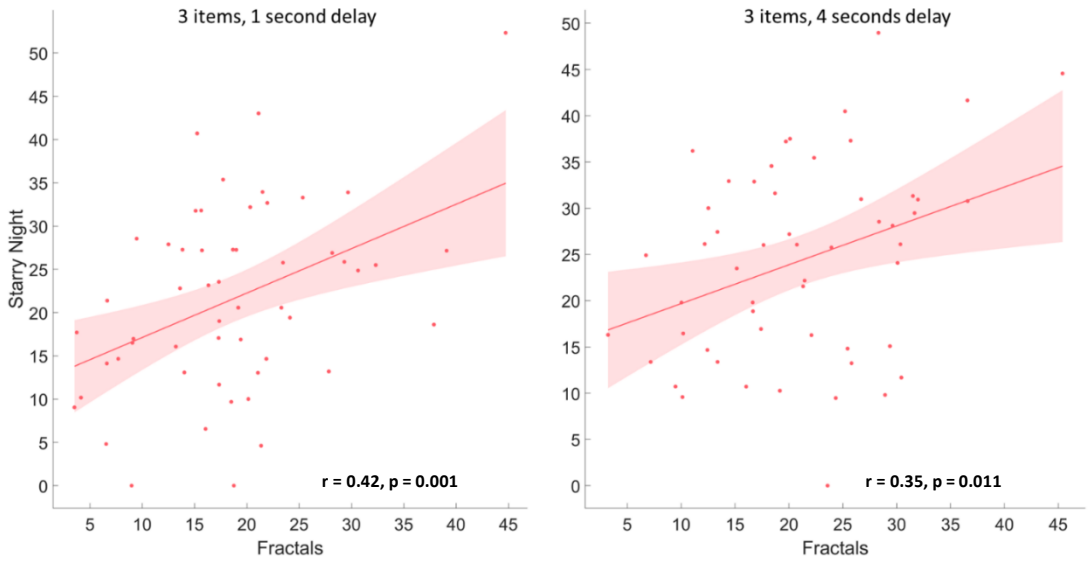


Figure 6.4 | Correlation of Misbinding between Starry Night and Fractals. Misbinding correlated between both tasks, for both delays.

Correlation of Misbinding in Starry Night and Hippocampal Volume

In order to investigate our hypothesis that Misbinding is linked to hippocampal volume, correlation analyses for Misbinding in conditions 3,4 and 6 and the volume of the left and right hippocampus were performed (**Fig. 6.5 and Fig. 6.6**).

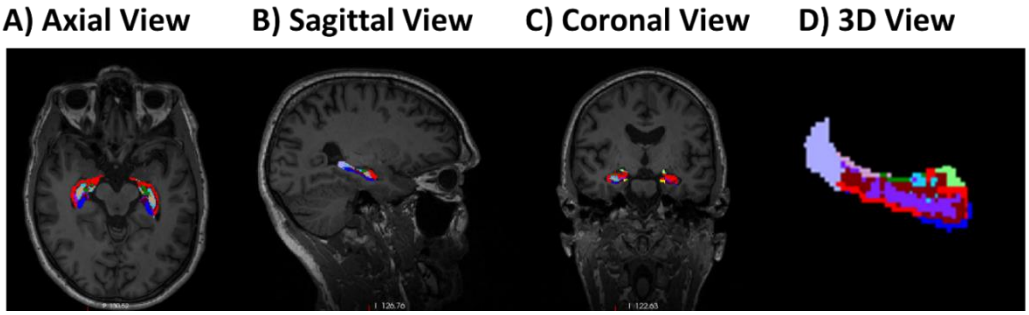


Figure 6.5 | The hippocampus and its subfields in one participant as segmented by the Freesurfer Pipeline. The hippocampal subfields were segmented and projected back on the original MRI scan (**A-C**). Panel **D** shows the 3D shape of the hippocampus.

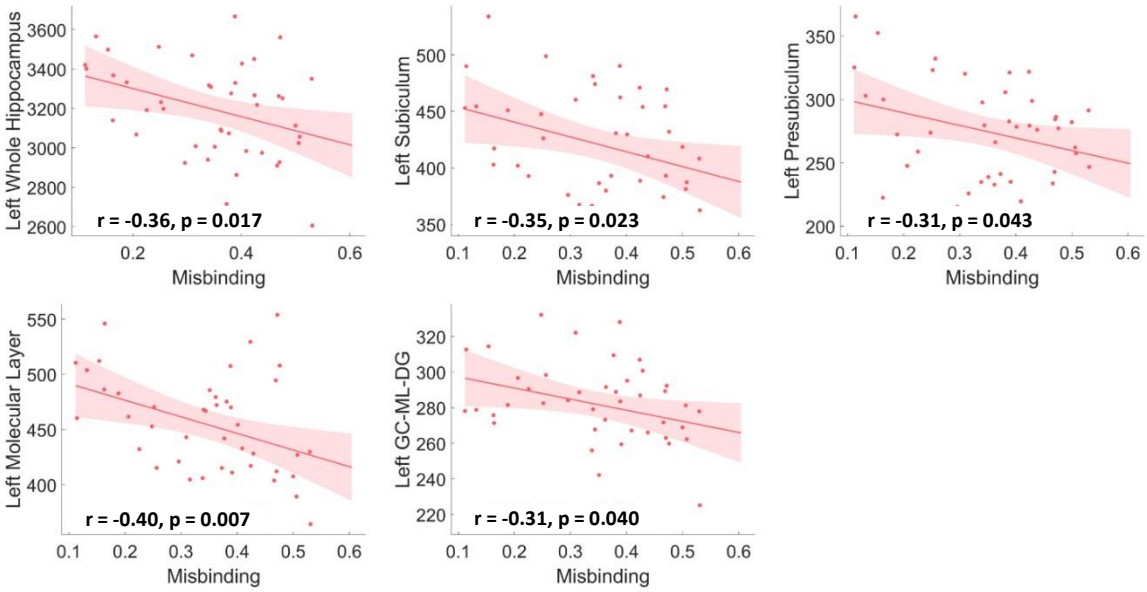


Figure 6.6 | Correlation of left hippocampus and hippocampal subfields and Misbinding in Starry Night trials with three items and a four second delay during which participants were to do the delay task. Misbinding in the most demanding condition correlated with left hippocampus and in particular with the left subiculum, presubiculum, molecular layer and the Granule Cell (GC) and Molecular Layer (ML) of the Dentate Gyrus (DG).

Only for Misbinding in the three-constellation trials with a delay task (condition 6) did we see a correlation with the left (r = -0.36, p = 0.017) but not the right hippocampal volume (r = -0.16, p = 0.313). Following up on this result, correlation analyses of the hippocampal subfields and Misbinding in this condition were performed. Misbinding in the most difficult condition was in particular correlated to the left subiculum (r = -0.35, p = 0.023), left presubiculum (r = -0.31, p = 0.043), the left molecular layer of the hippocampal tail (r = -0.40, p = 0.007) and the left GC-ML-DG (Granule Cell (GC) and Molecular Layer (ML) of the Dentate Gyrus (DG), r = -0.31, p = 0.040). The subiculum has previously been associated to short-term memory for spatial locations (Riegert et al., 2004) and the presubiculum volume has previously been proposed as a potential marker of imminent memory problems such as in people developing symptoms of Alzheimer's disease (Jacobs et al., 2020). The GC-ML-DG are known to be connected to mossy fibers which themselves terminate in the cornu ammonis 3 (Amaral et al., 2007) which has previously been linked to retrieval of spatial working memory (Song et al., 2020). The molecular layer houses the perforant path. Lesions of the perforant path have previously been linked to impairments in spatial short-term memory (Vago & Kesner, 2008).

Starry Night in different age groups

In a first step, a 2x2x2 repeated-measures ANOVA of set size, delay and group was performed in the Identification Accuracy, Localisation error and reaction time was performed in conditions 1-4 and a 2x2-ANOVA of delay and group was performed

in Misbinding, Guessing and Imprecision (**Fig. 6.7**). This analysis showed that an increase of the set size resulted in a decrease of the Identification Accuracy ($F(1,128) = 250.69$, $p < 0.001$, $\eta_p^2 = 0.662$) and an increase of the Localisation error ($F(1,128) = 934.37$, $p < 0.001$, $\eta_p^2 = 0.880$). A longer delay increased Guessing ($F(1,128) = 23.94$, $p < 0.001$, $\eta_p^2 = 0.158$) and Imprecision ($F(1,128) = 26.77$, $p < 0.001$, , $\eta_p^2 = 0.173$). There was an effect of the factor group in Misbinding ($F(2,128) = 5.75$, $p = 0.004$, $\eta_p^2 = 0.082$). Post-hoc t-tests confirmed these significant group differences for Misbinding: I.e., the group of young controls aged 18-30 years did significantly less misbinding than the group aged 30-50 ($t = 3.00$, $p = 0.010$) and the group of elderly controls ($t = 2.80$, $p = 0.012$). There was no such difference between volunteers aged 30-50 and elderly controls ($t = 0.64$, $p = 0.522$). There was an interaction of factors group and set size in the Localisation error ($F(2,128) = 14.95$, $p < 0.001$, $\eta_p^2 = 0.189$). Post-hoc tests confirmed that there was a delay effect in recruits aged 18-30 ($t = 14.22$, $p < 0.001$), in people aged 30-50 ($t = 16.32$, $p < 0.001$) and in elderly controls ($t = 23.82$, $p < 0.001$).

In the next step, a 2x2x3 repeated-measures ANOVA of factors delay task x set size x group was performed on four-second-delay trials only (**Fig. 6.8**). Details for this analysis can be found in **Supplementary Tables 6.1-6.10**. There was a significant main effect of the factor set size in the Identification Accuracy ($F(1,128) = 223.95$, $p < 0.001$, $\eta_p^2 = 0.636$), Localisation error ($F(1,128) = 1073.34$, $p < 0.001$, $\eta_p^2 = 0.893$) and Reaction Time ($F(1,128) = 57.82$, $p < 0.001$, $\eta_p^2 = 0.311$). When participants were to do an unrelated task during the delay, their Identification Accuracy was

lower (F(1,128) = 135.65, p < 0.001, η_p^2 =0.515), their Localisation error (F(1,128) = 162.26, p < 0.001, η_p^2 = 0.559), Misbinding (F(1,128) = 97.06, p < 0.001, η_p^2 = 0.431), Guessing (F(1,128) = 161.63, p < 0.001, , η_p^2 = 0.558) and Imprecision (F(1,128) = 213.09, p < 0.001, η_p^2 = 0.625). The factor group was significant in Guessing (F(1,128) = 4.14, p = 0.018, , η_p^2 = 0.061). Post-hoc t-tests in Guessing showed that people aged 18-30 reported significantly less random responses than elderly controls (t = 2.84, p = 0.016) but there was no difference compared to controls aged between 30-50 (t = 1.76, p = 0.163). There was also no difference between the latter two (t = 0.69, p = 0.495). There was an interaction of factors set size and group in the Localisation error (F(2,128) = 8.92, p < 0.001, η_p^2 = 0.122), of factors set size and interference task in the Reaction time (F(2,128) = 6.95, p = 0.009, η_p^2 = 0.052) and a three-way interaction in the Reaction time (F(2,128) = 5.55, p = 0.005, η_p^2 = 0.080). These interactions were followed up on in **Supplementary Tables 6.3,6.5,6.6 and 6.9**.

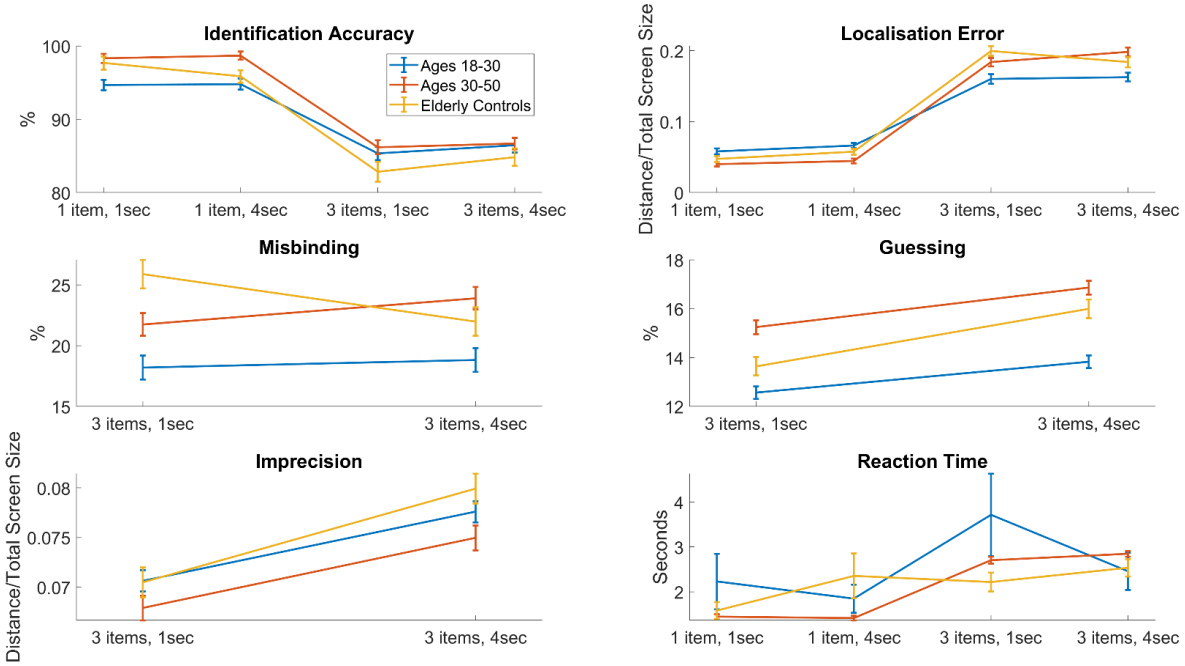


Figure 6.7 | Starry Night results across Age Groups in trials without a delay task. Groups performed very similar across all measures. However, the group of youngest volunteers aged 18-30 years showed significantly lower rates of Guessing and Misbinding.

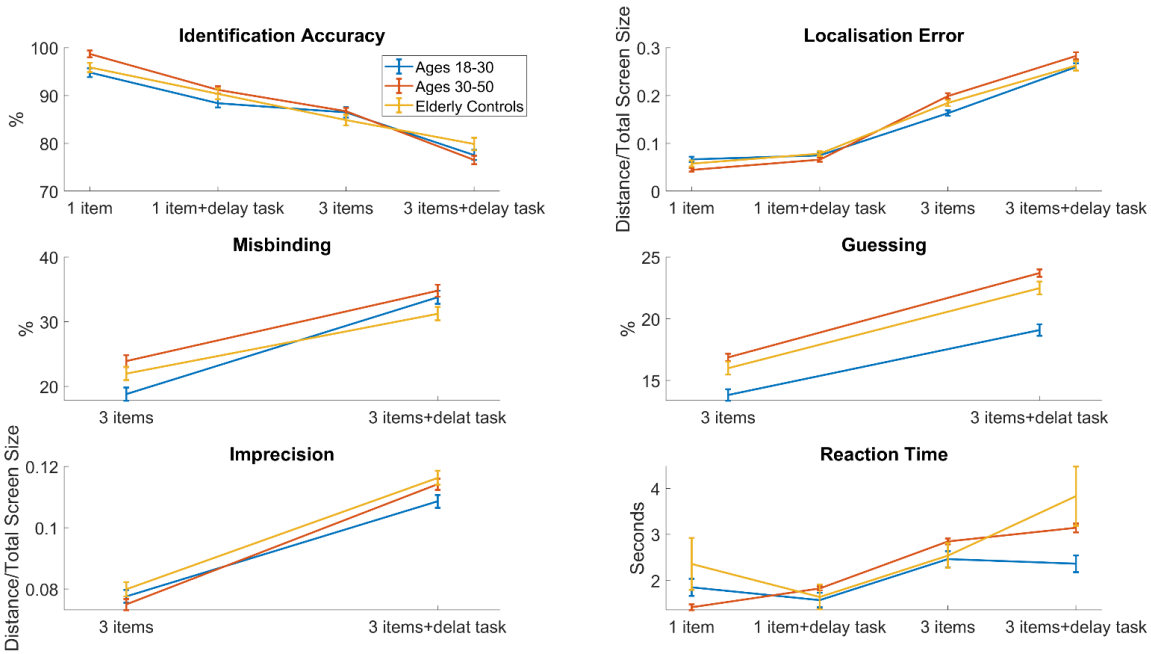


Figure 6.8 | Starry Night results across Age Groups in trials with a delay task. Even in the most demanding conditions, groups performed very similar across all measures. As for the other conditions, the group of youngest volunteers aged 18-30 years showed significantly lower rates of Guessing and Misbinding.

6.5 Discussion

In this study, a recently introduced task looking into hippocampal misbinding of features into objects was further developed and a gamified version created. In a first step, both tasks were tested in the target-age group which showed both tasks to present very similar results. That is, manipulations of delay and set size resulted in comparable effects on participants. In direct comparison, the task's most meaningful measure for a deficit in hippocampal feature binding, misbinding, showed to be significantly correlated between both tasks, the gamified and the lab-based version. It was in the most difficult condition of the gamified Starry Night task that there was a correlation between misbinding and the volume of the left hippocampus. In this condition, volunteers were to remember three items over a delay of four seconds during which they were to complete an unrelated task. Here, follow-up analyses showed that misbinding was particularly linked to the left subiculum, presubiculum, molecular layer and the GC-ML-DG. When Riegert et al. (2004) investigated behaviour of rats with electrolytic lesions of the ventral subiculum, they found that these would perform significantly worse in a water maze and radial-maze compared to the control group that only received sham lesions. The authors concluded that the subiculum is especially involved in working memory for spatial information. Besides this direct link between subiculum and spatial working memory, Jacobs et al. (2020) suggested the volume of the presubiculum to be a promising marker for development of Alzheimer's Disease in the future. In particular, they found the relationship between neocortical amyloid and memory to be mediated by presubiculum volume. However, in their task, the

authors used a list-learning exercise thus rather testing long-term instead of short-term memory. In the task presented in this thesis, misbinding shows to be correlated with the volume of the presubiculum suggesting that not only list-learning is related to this area, but object-location binding in short-term memory is too. The direct perforant path going through the GC-ML-DG inputs into the Cornu Ammonis Subregion of the CA1 and this connection has in the past been directly related to spatial working memory. I.e., Vago and Kesner (2008) show that disruption of this connection through local infusion of the non-selective dopamine agonist apomorphine into the CA1 led to short-term memory deficits in rats. The test results suggest that behavioural findings can be directly linked to volume of brain regions particularly involved in processing of spatial information. It is therefore important to compare the volumes of these hippocampal subregions between controls and AD patients in a next step in order to check if the results are consistent with the findings presented here.

Overall, participants of all groups performed at almost comparable levels with evidence for the youngest age group performing slightly better in the mixture model parameters than the other two groups which did, however, not manifest in the Localisation Performance. This will allow to distinguish healthy aging from pathologically increased misbinding in AD. Though the corona pandemic may have prevented the collection of data on AD patients for this study, evidence is clearly pointing towards the potential of using misbinding as an early cognitive marker in MCI and people at genetic risk of developing AD in the future (Toniolo et al., 2020).

6.6 Supplementary Materials

Supplementary Table 6.1: Repeated Measures ANOVA of set size, interference task and group in Identification Accuracy

Cases	Sum of Squares	df	Mean Square	F	p	η^2_p
Set size	1.539	1	1.539	223.950	< .001	0.636
Set size ✻ Group	0.037	2	0.018	2.682	0.072	0.040
Residuals	0.879	128	0.007			
Interference task	0.645	1	0.645	135.647	< .001	0.515
Interference task ✻ Group	0.025	2	0.013	2.649	0.075	0.040
Residuals	0.608	128	0.005			
Set size ✻ Interference task	0.007	1	0.007	2.020	0.158	0.016
Set size ✻ Interference task ✻ Group	0.005	2	0.003	0.763	0.468	0.012
Residuals	0.461	128	0.004			

Note. Type III Sum of Squares

Between Subjects Effects

Cases	Sum of Squares	df	Mean Square	F	p	η^2_p
Group	0.022	2	0.011	0.545	0.581	0.008
Residuals	2.585	128	0.020			

Note. Type III Sum of Squares

Supplementary Table 6.2: Repeated Measures ANOVA of set size, interference task and group in Localisation Performance

Cases	Sum of Squares	df	Mean Square	F	p	η^2_p
Set size	3.150	1	3.150	1073.338	< .001	0.893
Set size ✻ Group	0.052	2	0.026	8.923	< .001	0.122
Residuals	0.376	128	0.003			
Interference task	0.325	1	0.325	162.264	< .001	0.559
Interference task ✻ Group	2.260e-4	2	1.130e-4	0.056	0.945	8.808e-4
Residuals	0.256	128	0.002			
Set size ✻ Interference task	0.147	1	0.147	94.620	< .001	0.425
Set size ✻ Interference task ✻ Group	0.006	2	0.003	1.824	0.166	0.028
Residuals	0.199	128	0.002			

Note. Type III Sum of Squares

Between Subjects Effects

Cases	Sum of Squares	df	Mean Square	F	p	η^2_p
Group	0.005	2	0.002	0.449	0.639	0.007
Residuals	0.686	128	0.005			

Note. Type III Sum of Squares

Supplementary Table 6.3: Post Hoc Comparisons - Set size ✻ Interference task in Localisation Performance

		Mean Difference	SE	t	p_{holm}
one item, no interference	three items, no interference	-0.126	0.006	-20.759	< .001
	one item, interference	-0.017	0.005	-3.124	0.002

Supplementary Table 6.3: Post Hoc Comparisons - Set size ✻ Interference task in Localisation Performance

		Mean Difference	SE	t	p_{holm}
three items, no interference	three items, interference	-0.212	0.006	-33.371	< .001
	one item, interference	0.109	0.006	17.146	< .001
one item, interference	three items, interference	-0.086	0.005	-15.988	< .001
	three items, interference	-0.195	0.006	-32.211	< .001

Note. P-value adjusted for comparing a family of 6

Note. Results are averaged over the levels of: Group

Supplementary Table 6.4: Repeated Measures ANOVA of set size, interference task and group in Reaction Time

Cases	Sum of Squares	df	Mean Square	F	p	η^2_p
Set size	1.453e-4	1	1.453e-4	57.819	< .001	0.311
Set size ✻ Group	1.168e-5	2	5.841e-6	2.324	0.102	0.035
Residuals	3.216e-4	128	2.513e-6			
Interference task	2.769e-6	1	2.769e-6	0.738	0.392	0.006
Interference task ✻ Group	8.008e-6	2	4.004e-6	1.067	0.347	0.016
Residuals	4.802e-4	128	3.752e-6			
Set size ✻ Interference task	1.474e-5	1	1.474e-5	6.952	0.009	0.052
Set size ✻ Interference task ✻ Group	2.354e-5	2	1.177e-5	5.550	0.005	0.080
Residuals	2.714e-4	128	2.121e-6			

Note. Type III Sum of Squares

Between Subjects Effects

Cases	Sum of Squares	df	Mean Square	F	p	η^2_p
Group	2.049e-5	2	1.024e-5	2.736	0.069	0.041
Residuals	4.792e-4	128	3.744e-6			

Note. Type III Sum of Squares

Supplementary Table 6.5: Post Hoc Comparisons - Set size ✻ Interference task in Reaction Time

		Mean Difference	SE	t	p_{holm}
one item, no interference	three items, no interference	-7.419e-4	1.944e-4	-3.816	< .001
	one item, interference	1.965e-4	2.189e-4	0.898	0.370

Supplementary Table 6.5: Post Hoc Comparisons - Set size ✻ Interference task in Reaction Time

		Mean Difference	SE	t	p_{holm}
three items, no interference	three items, interference	-0.001	2.260e-4	-5.481	< .001
	one item, interference	9.383e-4	2.260e-4	4.151	< .001
one item, interference	three items, interference	-4.971e-4	2.189e-4	-2.271	0.048
	three items, interference	-0.001	1.944e-4	-7.384	< .001

Note. P-value adjusted for comparing a family of 6

Note. Results are averaged over the levels of: Group

Supplementary Table 6.6: Post Hoc Comparisons - Group ✻ Set size ✻ Interference task in Reaction Time

		Mean Difference	SE	t	p_{holm}
100, one item, no interference	200, one item, no interference	4.323e-4	3.486e-4	1.240	1.000
	1600, one item, no interference	-5.080e-4	4.104e-4	-1.238	1.000
	100, three items, no interference	-6.130e-4	3.209e-4	-1.910	1.000
	200, three items, no interference	-9.990e-4	3.486e-4	-2.866	0.204
	1600, three items, no interference	-6.893e-4	4.104e-4	-1.679	1.000
	100, one item, interference	2.772e-4	3.612e-4	0.767	1.000
	200, one item, interference	2.729e-5	3.486e-4	0.078	1.000
	1600, one item, interference	2.092e-4	4.104e-4	0.510	1.000

Supplementary Table 6.6: Post Hoc Comparisons - Group ✻ Set size ✻ Interference task in Reaction Time

		Mean Difference	SE	t	p_{holm}
	100, three items, interference	-5.120e-4	3.731e-4	-1.372	1.000
	200, three items, interference	-0.001	3.486e-4	-3.714	0.013
	1600, three items, interference	-0.002	4.104e-4	-4.838	< .001
200, one item, no interference	1600, one item, no interference	-9.403e-4	3.940e-4	-2.387	0.730
	100, three items, no interference	-0.001	3.486e-4	-2.998	0.140
	200, three items, no interference	-0.001	2.876e-4	-4.976	< .001
	1600, three items, no interference	-0.001	3.940e-4	-2.847	0.212
	100, one item, interference	-1.550e-4	3.486e-4	-0.445	1.000
	200, one item, interference	-4.050e-4	3.238e-4	-1.251	1.000
	1600, one item, interference	-2.231e-4	3.940e-4	-0.566	1.000
	100, three items, interference	-9.442e-4	3.486e-4	-2.709	0.315
	200, three items, interference	-0.002	3.345e-4	-5.164	< .001
	1600, three items, interference	-0.002	3.940e-4	-6.137	< .001
1600, one item, no interference	100, three items, no interference	-1.050e-4	4.104e-4	-0.256	1.000
	200, three items, no interference	-4.910e-4	3.940e-4	-1.246	1.000

Supplementary Table 6.6: Post Hoc Comparisons - Group ✻ Set size ✻ Interference task in Reaction Time

		Mean Difference	SE	t	p_{holm}
	1600, three items, no interference	-1.813e-4	3.930e-4	-0.461	1.000
	100, one item, interference	7.852e-4	4.104e-4	1.913	1.000
	200, one item, interference	5.353e-4	3.940e-4	1.359	1.000
	1600, one item, interference	7.172e-4	4.424e-4	1.621	1.000
	100, three items, interference	-3.970e-6	4.104e-4	-0.010	1.000
	200, three items, interference	-7.868e-4	3.940e-4	-1.997	1.000
	1600, three items, interference	-0.001	4.570e-4	-3.234	0.072
100, three items, no interference	200, three items, no interference	-3.861e-4	3.486e-4	-1.107	1.000
	1600, three items, no interference	-7.631e-5	4.104e-4	-0.186	1.000
	100, one item, interference	8.902e-4	3.731e-4	2.386	0.730
	200, one item, interference	6.403e-4	3.486e-4	1.837	1.000
	1600, one item, interference	8.222e-4	4.104e-4	2.003	1.000
	100, three items, interference	1.010e-4	3.612e-4	0.280	1.000
	200, three items, interference	-6.819e-4	3.486e-4	-1.956	1.000
	1600, three items, interference	-0.001	4.104e-4	-3.345	0.047
200, three items, no interference	1600, three items, no interference	3.098e-4	3.940e-4	0.786	1.000

Supplementary Table 6.6: Post Hoc Comparisons - Group ✻ Set size ✻ Interference task in Reaction Time

		Mean Difference	SE	t	p_{holm}
	100, one item, interference	0.001	3.486e-4	3.661	0.015
	200, one item, interference	0.001	3.345e-4	3.069	0.120
	1600, one item, interference	0.001	3.940e-4	3.067	0.117
	100, three items, interference	4.871e-4	3.486e-4	1.397	1.000
	200, three items, interference	-2.958e-4	3.238e-4	-0.913	1.000
	1600, three items, interference	-9.867e-4	3.940e-4	-2.504	0.554
1600, three items, no interference	100, one item, interference	9.665e-4	4.104e-4	2.355	0.757
	200, one item, interference	7.166e-4	3.940e-4	1.819	1.000
	1600, one item, interference	8.985e-4	4.570e-4	1.966	1.000
	100, three items, interference	1.773e-4	4.104e-4	0.432	1.000
	200, three items, interference	-6.056e-4	3.940e-4	-1.537	1.000
	1600, three items, interference	-0.001	4.424e-4	-2.930	0.178
100, one item, interference	200, one item, interference	-2.499e-4	3.486e-4	-0.717	1.000
	1600, one item, interference	-6.802e-5	4.104e-4	-0.166	1.000
	100, three items, interference	-7.892e-4	3.209e-4	-2.459	0.627

Supplementary Table 6.6: Post Hoc Comparisons - Group ✻ Set size ✻ Interference task in Reaction Time

		Mean Difference	SE	t	p_{holm}
	200, three items, interference	-0.002	3.486e-4	-4.510	< .001
	1600, three items, interference	-0.002	4.104e-4	-5.514	< .001
200, one item, interference	1600, one item, interference	1.819e-4	3.940e-4	0.462	1.000
	100, three items, interference	-5.393e-4	3.486e-4	-1.547	1.000
	200, three items, interference	-0.001	2.876e-4	-4.596	< .001
	1600, three items, interference	-0.002	3.940e-4	-5.109	< .001
1600, one item, interference	100, three items, interference	-7.212e-4	4.104e-4	-1.757	1.000
	200, three items, interference	-0.002	3.940e-4	-3.818	0.009
	1600, three items, interference	-0.002	3.930e-4	-5.585	< .001
100, three items, interference	200, three items, interference	-7.829e-4	3.486e-4	-2.246	0.982
	1600, three items, interference	-0.001	4.104e-4	-3.591	0.020
200, three items, interference	1600, three items, interference	-6.909e-4	3.940e-4	-1.754	1.000

Note. P-value adjusted for comparing a family of 66

Supplementary Table 6.7: Repeated Measures ANOVA of interference task and group in Misbinding

Cases	Sum of Squares	df	Mean Square	F	p	η^2_p
Inteference task	0.838	1	0.838	97.056	< .001	0.431
Inteference task ✻ Group	0.034	2	0.017	1.994	0.140	0.030
Residuals	1.105	128	0.009			

Note. Type III Sum of Squares

Between Subjects Effects

Cases	Sum of Squares	df	Mean Square	F	p	η^2_p
Group	0.055	2	0.028	1.733	0.181	0.026
Residuals	2.039	128	0.016			

Note. Type III Sum of Squares

Supplementary Table 6.8: Repeated Measures ANOVA of interference task and group in Guessing

Cases	Sum of Squares	df	Mean Square	F	p	η^2_p
Interference task	0.235	1	0.235	161.628	< .001	0.558
Interference task ✻ Group	0.003	2	0.002	1.149	0.320	0.018
Residuals	0.186	128	0.001			

Note. Type III Sum of Squares

Between Subjects Effects

Cases	Sum of Squares	df	Mean Square	F	p	η^2_p
Group	0.075	2	0.038	4.144	0.018	0.061
Residuals	1.162	128	0.009			

Note. Type III Sum of Squares

Supplementary Table 6.9: Post Hoc Comparisons - Group in Guessing

		Mean Difference	SE	t	p_{holm}
18-30	>50	-0.038	0.013	-2.840	0.016
	30-50	-0.028	0.016	-1.755	0.163
>50	30-50	0.010	0.015	0.685	0.495

Note. P-value adjusted for comparing a family of 3

Note. Results are averaged over the levels of: Interference task

Supplementary Table 6.10: Repeated Measures ANOVA of interference task and group in Imprecision

Cases	Sum of Squares	df	Mean Square	F	p	η^2_p
Interference task	0.077	1	0.077	213.094	< .001	0.625
Interference task ✻ Group	8.539e-4	2	4.270e-4	1.176	0.312	0.018
Residuals	0.046	128	3.630e-4			

Note. Type III Sum of Squares

Between Subjects Effects

Cases	Sum of Squares	df	Mean Square	F	p	η^2_p
Group	9.250e-4	2	4.625e-4	0.455	0.635	0.007
Residuals	0.130	128	0.001			

Note. Type III Sum of Squares

7. General Discussion

7.1 Summary

In this thesis, critical gaps in our understanding of binding and attention in short-term memory were identified and examined in five empirical chapters.

The first chapter explored the effects of probe interference in short-term memory. For this purpose, a *bare* probe was introduced that did not hold any additional information on the dimension that was probed. I.e., instead of asking participants to reproduce an orientation starting off with a random orientation that was to be rearranged, they started off with a dot in the colour of the arrow that was to be reproduced. In line with our hypothesis of pattern-completion recall, participants performed significantly better when presented only with the colour they were asked to reproduce the arrow of. This was true even after *perceptual* masking, thus, the effect could not be reduced to the advantage of a purely perceptual buffer that was overwritten when novel information such as the probe was presented. However, there was no advantage of a bare probe over a compound probe that held information that was not needed to perform the task when the item probed was the last item of a sequence. It was, therefore, concluded that items that profit from the recency effect do not require reactivation through pattern completion. The last item of a sequence might rather be in a more readily available state than previous items, a state that was in the past associated with an item being held in the *focus of attention*.

Yet in the past, the literature discussed two distinct mechanisms underlying an item being moved into this focus of attention. Besides the previously discussed recency effect, another possibility of moving information into the focus of attention might be retro-cueing. Hence, cues pointing towards one of several items could move said item into the focus of attention and could also reduce the chance of probe interference occurring for this item.

To compare the previously observed effects, we conducted a follow up experiment using the same paradigm of a bare probe in an incidental retro-cue experiment. Here, items that were retro-cued to were remembered faster and more precisely than those that were not retro-cued to. However, there was somewhat of a difference in these items' susceptibility towards probe interference. Unlike items that were moved into the focus of attention through recency, incidental retro-cueing did not protect items from probe interference. That is, there was no advantage of the bare probe compared to the compound probe for a retro-cued item. Also, the process of double retro-cueing was not able to reproduce a recency effect. I.e., when a first retro-cue was invalid and the second retro-cue valid, this did not lead to a benefit comparable to an actual sequential presentation of items in the first place. Further, there was hardly any evidence for recency and retro-cue to be additive effects. They rather showed to be two distinct mechanisms.

Given the general susceptibility of visual short-term memory experiments towards probe interference, a need for a probe-free task was identified. Thus, in a next step, an experiment was introduced in which participants were able to directly

reproduce features without the need to use a visual cue. I.e., objects containing of two features were to be reproduced on both their dimensions. In the case presented in this thesis, colours as well as locations of objects were to be reproduced. Given that the experimenter shares the participant's insecurity of which item was reproduced when several items were presented, a new probabilistic model based on the mixture model of error sources in continuous reproduction tasks was introduced. This model further revealed another problem, previous experiments were not able to fully explore. Swap errors that are defined as being an unintended amnestic exchange of features of two distinct objects for one another, might in fact not always be symmetrical. Hence, though the experiment suggests one object's feature to be replaced with another, it remains unclear whether these two items really replace one another. The reason for this uncertainty is that the fate of only one item is tested in short-term memory experiments that do not require full report of all information previously presented. Moreover, only an experiment that requires all the object's features to be reproduced can ultimately determine binding between features. I.e., though two features of two distinct objects might take each other's spot in the mind's representation, it remains unclear whether the remaining features of a two-feature object are in fact correctly recalled or whether guessing happened on one of these. The novel mixture model presented in this thesis accounts not only for symmetric but also for asymmetric swaps. Moreover, it manages to distinguish between guessing on features versus the whole object. Further, it unravels differences of the frequency of guessing in swapped versus non-swapped features.

Though the type of probing in the third experiment shows potential to avoid interference caused by the probe itself, the mechanisms of moving items in and out of the focus of attention where they could be protected from interference, such as the interference caused by the probe itself, remain at the centre of further clinical research interest. That is because different cognitive diseases might affect different parts of visual short-term memory and thus in some patients, the ability to move information in and out of the focus of attention might in particular be impaired and consequently, treatment of impairment should focus on stabilizing the focus of attention. In this thesis, Parkinson's Disease Dementia was identified as one such disease a symptom of which is an impaired ability to focus attention based on a cortical lack of acetylcholine. Patients on and off their treatment with cholinesterase inhibitors were tested on a short-term memory task that required them to move information in and out of the focus of attention.

The results show a clear effect of the drug for the benefit of participants' short-term memory. The chapter was able to show that this effect could not be pinned to a cholinergic effect on retention. Nor did Rivastigmine stabilize the patient's mental image. The results presented here rather suggest the cholinesterase inhibitor to improve encoding, retrieval and/or the general fluctuation of attention.

Despite such promising results, the fifth and final empirical chapter of this thesis introduces the idea of how important early detection of severe cognitive impairment is. Given that cognitive impairment linked to pathologic aging will

have a deep impact on our aging society and economy, an easy-to-use tool is required to identify individuals at early stages of disease in order to change their trajectory.

Therefore, the fifth chapter introduced a gamified test using a novel behavioural marker of hippocampal dysfunction, *misbinding*. The degree to which participants confuse the features of two distinct objects on one dimension with one another is directly linked to the hippocampus. In the experiment presented, participants were to remember the locations and appearances of several random star constellations. If they were dragging a star constellation towards the location of another originally presented star constellation, this counted as a trial in which they misbound. Notably, participants of different age groups performed similarly suggesting that increased misbinding is a pathology linked to pathologic aging whereas it does not necessarily affect healthy aging. Though the circumstances surrounding the coronavirus pandemic in the years of 2020 and 2021 had an impact on recruitment of patients suffering from Alzheimer's disease, this thesis could at least provide a large sample of healthy people of different age groups. Yet, in a next step, this should be expanded on patient groups in order to prove the functionality of the test.

In summary, this thesis shows that retrieval through pattern completion is significantly affected by additional information on the dimension at probe that is not needed to solve the task itself. Recency protects information from this detrimental effect, but retro-cueing does not. Both, retro-cueing and recency improve participants' performance in short-term memory tasks. Yet, these effects

are not additive and given the discrepancy in protection from probe interference, the results show that the way an item is moved into the focus of attention has a direct impact on its representation. The focus of attention is not directly susceptible by acetylcholine, but cholinesterase inhibitors improve short-term memory in general which makes them a drug with a lot of potential in patients suffering from acetylcholine deficit, such as patients suffering from Parkinson's disease dementia.

Interference caused by probe can be eliminated using an experiment that does not use a cue that needs to be adjusted. Such experiment also reveals the fate of both dimensions of several two-dimensional objects and thus makes an essential differentiation between misbinding and swap errors. Where the latter can be a symmetrical exchange of information on the same dimension between two objects, the former simply describes one feature to be exchanged with another object's feature. Misbinding as such is a cognitive marker of hippocampal function. It can thus be used to track pathologic changes in memory performance while healthy aging affects misbinding only marginally.

But there are still some open questions unravelled by this thesis that will require further research in the future.

7.2 Open Questions and Outlook on the focus of attention

Despite the fact that this thesis could contribute to the overall understanding of items entering the focus of attention (i.e. in terms of being remembered faster, more precisely or being protected from interference), the purpose of the focus of attention is not yet quite understood. The features pointed out in this thesis and in previous research make it obvious that items in the focus of attention are in a prioritized state that allows for overall improved recall and protection of information. Yet, daily struggles not only require us to remember things important to our train of thoughts quickly and precisely but often enough require us to flexibly manipulate this information. For example, flexible navigation in a changing context will not only require recovery of retrospective information but would require the information to be adapted in the current context. This would intuitively require such information retrieved from short-term memory to be fluid in a way that allows manipulation while keeping the essentials in a way that allows pure retrieval such as tested in most short-term memory experiments. However, with this somewhat intuitive idea of information stored in the focus of attention, a pressing question is whether fluidity could as well lead to a loss of parts of information. Such questions should be addressed in future research of the focus of attention.

In general, this thesis showed somewhat ambiguous results looking at recency and how it related to moving items into the focus of attention. The first empirical chapter showed only little evidence for the last item of a sequence being protected from interference (i.e., no interaction but insignificant t-test). A lack of reaction

time benefit for the last item together with rather ambiguous results in the absolute error suggest that the last item in the sequence might not be in the focus of attention at the time of probing. Or, it might in some trials be in the focus of attention and in others it might not, explaining why the last item in the sequence shows a benefit in overall absolute error but no protection from interference. Potentially, participants might have already started rehearsing the sequence by the time of probing, thus, other items would compete for the focus of attention at the cost of the final item of the sequence. The last-presented item does not show a response-time benefit over earlier items which could further point at the fact that it is no longer in the focus of attention. Future research should investigate these hypotheses by testing different delay periods in the paradigms shown here. Another possibility would be that recency and retro-cueing lead to different functional states within the focus of attention. A state the item could be *tagged* with through the task set. I.e., a retro-cue might to some extend imply that the item is to be used *and* mentally modified in a further step whereas this might not be the case with the last item in the sequence. In addition, items stored in an activity-silent synaptic state might be stored with different precision. Thus, within this state, some items might be recalled better than others.

In terms of the gamified memory task, further consideration of when misbinding occurs should be involved. I.e., Tabi et al. recently discovered that manipulations during encoding, maintenance and retrieval impact on participants' performance independently from one another (Tabi et al., 2021). In this paper, two experiments

were performed. In the first one, participants were presented with two or three circles for a short period of time. All of the stimuli were presented on the half of the screen a central arrow pointed towards. That is except for the condition with three items where in half of the trials, only two items were presented on the screen half the arrow pointed towards and the third one was presented on the other side. Only the items presented on the screen half the arrow pointed towards were to be remembered, other items were to be ignored. Besides this manipulation of processing demands during encoding, the second manipulation of processing demands happened during retrieval: The circular stimuli used in the experiment consisted of two differently coloured semicircles. At retrieval, a foil was presented together with the probe that either consisted of one or two colours that were previously presented in the encoding display. Participants were to select the target and drag it to its original location. In the second experiment which focused on the manipulation of processing demands during maintenance, items were presented followed by a maintenance interval during which participants were either presented with items they were to ignore or they were to remember instead of the items originally presented. In the future, the gamified task presented in this thesis should be adapted in order to find the manipulation, i.e. during encoding, maintenance or retrieval, that *amplifies* misbinding the most. For this purpose, participants suffering from Alzheimer's disease or from Mild Cognitive Impairment should be tested on the task presented by Tabi et al (2021). This kind of test might also be suitable to investigate whether patients' ability to ignore information during encoding, maintenance and retrieval deteriorates at the same or at different pace while the disease progresses over time. In particular, in

terms of dealing with a general increase of attentional demands, there has been some evidence that very early impairment in MCI is associated to higher neuronal activation in the frontostriatal network in a divided attention task which has been interpreted as a sign of neuroplasticity: In their study, Clements et al. show that MCI with relatively low cognitive impairment performed at similar levels as controls when solving alphanumeric equations while attending to a colour patch a colour-change of which was to be reported (Clément et al., 2013). The authors also asked participants to do a manipulation task in which volunteers were to monitor and manipulate the alphabet while solving alphanumeric equations. Here, however, participants' performance was generally significantly worse compared to controls, even in MCI patients with lower degrees of cognitive impairment. In their review, Kirova and colleagues (Kirova et al., 2015) point out that this could be a possible sign of manipulation capabilities deteriorating earlier than the ability to divide attention. Yet, the data does not allow us to determine whether this is true for attentional demands during encoding, maintenance and retrieval. Furthermore, only an analogue report measure that assess errors of feature binding would allow to determine the origin of such effects, be it errors of binding or random noise.

7.3 Final Remarks

Here, five different chapters have been presented suggesting different approaches that should be taken into account in the future of short-term memory research. In particular, future studies should consider the effects of the memory probe itself. One approach would be to adopt a technique commonly used in long-term memory research, namely an experimental setting without a probe.

Also, this thesis suggests that prioritization in short-term memory heavily depends on the way items are moved into the focus of attention. Though recency and incidental retro-cueing both improve performance within tasks, only recency protects items from probe interference.

Setting findings from short-term memory into a clinical context, the results presented here show that positive effects of acetylcholine can be tracked down to remembering information over short periods of time, most likely linked to an improvement of encoding, retrieval or the reduction of attentional fluctuations. Moreover, new gamified tablet tests are able to reflect function of small brain areas, like the hippocampus, that are linked to an early affection in Alzheimer's disease.

8. References

2016 Alzheimer's disease facts and figures. (2016). *Alzheimer's & Dementia : The Journal of the Alzheimer's Association*, *12*(4), 459–509. https://doi.org/10.1016/j.jalz.2016.03.001

Adam, K. C. S., Doss, M. K., Pabon, E., Vogel, E. K., & de Wit, H. (2020). Δ9-Tetrahydrocannabinol (THC) impairs visual working memory performance: a randomized crossover trial. *Neuropsychopharmacology*, *45*(11), 1807–1816. https://doi.org/10.1038/s41386-020-0690-3

Adam, K. C. S., & Vogel, E. K. (2018). Improvements to visual working memory performance with practice and feedback. *PLoS ONE*, *13*(8), 1–22. https://doi.org/10.1371/journal.pone.0203279

Aggleton, J. P., & Brown, M. W. (2006). Interleaving brain systems for episodic and recognition memory. *Trends in Cognitive Sciences, 10*(10), 455–463. https://doi.org/10.1016/j.tics.2006.08.003

Allen, R. J., Baddeley, A. D., & Hitch, G. J. (2006). Is the binding of visual features in working memory resource-demanding? *Journal of Experimental Psychology: General*, *135*(2), 298–313. https://doi.org/10.1037/0096-3445.135.2.298

Amaral, D. G., Scharfman, H. E., & Lavenex, P. (2007). The dentate gyrus: fundamental neuroanatomical organization (dentate gyrus for dummies). *Progress in Brain Research*, *163*, 3–22. https://doi.org/10.1016/S0079-6123(07)63001-5

Astle, D. E., Summerfield, J., Griffin, I., & Nobre, A. C. (2012). Orienting attention to locations in mental representations. *Attention, Perception, and Psychophysics*, *74*(1), 146–162. https://doi.org/10.3758/s13414-011-0218-3

Atkinson, R. C., & Shiffrin, R. M. (1968). Human Memory: A proposed system and its control processes BT - The Psychology of Learning and Motivation. *The Psychology of Learning and Motivation*, *2*(5), 89–195.

Baddeley, A. (2012). Working memory: Theories, models, and controversies. *Annual Review of Psychology*, *63*, 1–29. https://doi.org/10.1146/annurev-psych-120710-100422

Baddeley, A. D., & Hitch, G. (1974). *Working Memory*, *8*, 47–89. Academic Press. https://doi.org/https://doi.org/10.1016/S0079-7421(08)60452-1

Bateman, R. J., Xiong, C., Benzinger, T. L. S., Fagan, A. M., Goate, A., Fox, N. C., Marcus, D. S., Cairns, N. J., Xie, X., Blazey, T. M., Holtzman, D. M., Santacruz, A., Buckles, V., Oliver, A., Moulder, K., Aisen, P. S., Ghetti, B., Klunk, W. E., McDade, E., … Morris, J. C. (2012). Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease. *New England Journal of Medicine*, *367*(9), 795–804. https://doi.org/10.1056/NEJMoa1202753

Bays, P. M., Catalao, R. F. G., & Husain, M. (2009). The precision of visual working memory is set by allocation of a shared resource. *Journal of Vision*, *9*(10), 1–11. https://doi.org/10.1167/9.10.7

Bays, P. M., Catalao, R. F. G., & Husain, M. (2011). *The precision of visual working memory is set by allocation of a shared resource*. *9*(10), 1–14. https://doi.org/10.1167/9.10.7.

Bays, P. M., & Husain, M. (2008). Dynamic shifts of limited working memory resources in human vision. *Science*, *321*(5890), 851–854. https://doi.org/10.1126/science.1158023

Bays, P. M., Wu, E. Y., & Husain, M. (2011). *Storage and binding of object features in visual working memory*. *49*(6), 1622–1631. https://doi.org/10.1016/j.neuropsychologia.2010.12.023.Storage

Bentley, P. (2011). *Effects of cholinesterase inhibition on brain function*.

Bentley, P., Driver, J., & Dolan, R. J. (2008). Cholinergic modulation of visual and attentional brain responses in Alzheimer ' s disease and in health. *Brain*, *131*(2), 409–424. https://doi.org/10.1093/brain/awm299.Cholinergic

Bentley, P., Husain, M., & Dolan, R. J. (2004). Effects of Cholinergic Enhancement on Visual Stimulation, Spatial Attention, and Spatial Working Memory. *Neuron*, *41*(6), 969–982. https://doi.org/https://doi.org/10.1016/S0896-6273(04)00145-X

Berdyyeva, T. K., & Olson, C. R. (2016). *Intracortical Microstimulation of the Supplementary Eye Field Impairs the Ability of Monkeys to Make Serially Ordered Saccades . Intracortical microstimulation of supplementary eye field impairs ability of monkeys to make serially ordered saccades*. https://doi.org/10.1152/jn.00503.2013

Berke, J. D. (2018). What does dopamine mean? *Nature Neuroscience*, *21*(6), 787–793. https://doi.org/10.1038/s41593-018-0152-y

Blalock, L. D., & Clegg, B. A. (2010). Encoding and representation of simultaneous and sequential arrays in visuospatial working memory. *Quarterly Journal of Experimental Psychology*, *63*(5), 856–862.

Bohnen, N. I., & Albin, R. L. (2011). The cholinergic system and Parkinson disease. *Behavioural Brain Research*, *221*(2), 564–573. https://doi.org/10.1016/j.bbr.2009.12.048

Bohnen, N. I., Kaufer, D. I., Hendrickson, R., Ivanco, L. S., Lopresti, B. J., Constantine, G. M., Mathis, C. A., Davis, J. G., Moore, R. Y., & Dekosky, S. T. (2006). *Cognitive correlates of cortical cholinergic denervation in Parkinson ' s disease and parkinsonian dementia*. 242–247. https://doi.org/10.1007/s00415-005-0971-0

Braak, H., Braak, E., & Bohl, J. (1993). Staging of Alzheimer-related cortical destruction. *European Neurology*, *33*(6), 403–408. https://doi.org/10.1159/000116984

Brown, L. A., & Brockmole, J. R. (2010). The role of attention in binding visual features in working memory: Evidence from cognitive ageing. *Quarterly Journal of Experimental Psychology*, *63*(10), 2067–2079. https://doi.org/10.1080/17470211003721675

Calabresi, P., Picconi, B., Parnetti, L., & Di Filippo, M. (2006). A convergent model for cognitive dysfunctions in Parkinson's disease: the critical dopamine-acetylcholine synaptic balance. *The Lancet. Neurology*, *5*(11), 974–983. https://doi.org/10.1016/S1474-4422(06)70600-7

Candy, J. M., Perry, R. H., Perry, E. K., Irving, D., Blessed, G., Fairbairn, A. F., & Tomlinson, B. E. (1983). Pathological changes in the nucleus of meynert in Alzheimer's and Parkinson's diseases. *Journal of the Neurological Sciences*, *59*(2), 277–289. https://doi.org/https://doi.org/10.1016/0022-510X(83)90045-X

Clément, F., Gauthier, S., & Belleville, S. (2013). Executive functions in mild cognitive impairment: Emergence and breakdown of neural plasticity. *Cortex*, *49*(5), 1268–1279. https://doi.org/https://doi.org/10.1016/j.cortex.2012.06.004

Conrad, R. (1965). Order error in immediate recall of sequences. *Journal of Verbal Learning and Verbal Behavior*, *4*(3), 161–169. https://doi.org/10.1016/S0022-5371(65)80015-9 M4 - Citavi

Coughlan, G., Coutrot, A., Khondoker, M., Minihane, A.-M., Spiers, H., & Hornberger, M. (2019). Toward personalized cognitive diagnostics of at-genetic-risk Alzheimer's disease. *Proceedings of the National Academy of Sciences*, *116*(19), 9285–9292. https://doi.org/10.1073/pnas.1901600116

Cowan, N. (2016). *Working memory capacity: Classic edition*. Routledge.

Craik, F. I. M., & Lockhart, R. S. (1972). Levels of processing: A framework for memory research. *Journal of Verbal Learning and Verbal Behavior*, *11*(6), 671–684. https://doi.org/10.1016/S0022-5371(72)80001-X

Crow, T. J., & Grove-White, I. G. (1973). An analysis of the learning deficit following hyoscine administration to man. *British Journal of Pharmacology*, *49*(2), 322–327. https://doi.org/10.1111/j.1476-5381.1973.tb08379.x

Cuthbert, B., & Standage, D. (2018). *On the Short-Lived Nature of Working Memory : Drift and Decay in a Population-coding model*. *38*(48), 10241–10243.

deBettencourt, M. T., Keene, P. A., Awh, E., & Vogel, E. K. (2019). Real-time triggering reveals concurrent lapses of attention and working memory. *Nature Human Behaviour*, *3*(8). https://doi.org/10.1038/s41562-019-0606-6

Decker, A. L., & Duncan, K. (2020). ScienceDirect Acetylcholine and the complex interdependence of memory and attention. *COBEHA*, *32*, 21–28. https://doi.org/10.1016/j.cobeha.2020.01.013

Deco, G., Jirsa, V. K., Robinson, P. A., Breakspear, M., & Friston, K. (2008). The dynamic brain: From spiking neurons to neural masses and cortical fields. *PLoS Computational Biology*, *4*(8). https://doi.org/10.1371/journal.pcbi.1000092

Doesburg, S. M., Ribary, U., Herdman, A. T., Miller, S. P., Poskitt, K. J., Moiseev, A., Whitfield, M. F., Synnes, A., & Grunau, R. E. (2011). Altered long-range alpha-band synchronization during visual short-term memory retention in children born very preterm. *NeuroImage*, *54*(3), 2330–2339. https://doi.org/10.1016/j.neuroimage.2010.10.044

Donkin, C., & Nosofsky, R. M. (2012). A Power-Law Model of Psychological Memory Strength in Short- and Long-Term Recognition. *Psychological Science*, *23*(6), 625–634. https://doi.org/10.1177/0956797611430961

Dubois, B., Ruberg, M., Javoy-Agid, F., Ploska, A., & Agid, Y. (1983). A subcortico-cortical

cholinergic system is affected in Parkinson's disease. *Brain research*, *288*(1-2), 213–218. https://doi.org/10.1016/0006-8993(83)90096-3

Duncan, J., Parr, A., Woolgar, A., Thompson, R., Bright, P., Cox, S., Bishop, S., & Nimmo-Smith, I. (2008). Goal neglect and Spearman's g: competing parts of a complex task. *Journal of Experimental Psychology: General*, *137*(1), 131.

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

Engle, R. W., & Kane, M. J. (2003). Executive Attention, Working Memory Capacity, and a Two-Factor Theory of Cognitive Control. *Psychology of Learning and Motivation - Advances in Research and Theory*, *44*, 145–199. https://doi.org/10.1016/S0079-7421(03)44005-X

Fallon, Sean J, Mattiesing, R. M., Dolfen, N., Manohar, S. G., & Husain, M. (2018). ScienceDirect Ignoring versus updating in working memory reveal differential roles of attention and feature. *CORTEX*, *107*, 50–63. https://doi.org/10.1016/j.cortex.2017.12.016

Fallon, Sean James, Mattiesing, R. M., Muhammed, K., Manohar, S., & Husain, M. (2017). Fractionating the neurocognitive mechanisms underlying working memory: Independent effects of dopamine and Parkinson's disease. *Cerebral Cortex*, *27*(12), 5727–5738. https://doi.org/10.1093/cercor/bhx242

Farrell, L., & Stephan, L. (2002). An endogenous distributed model of ordering in serial recall. *Psychonomic Bulletin & Review*, *9*, 59–79.

Fougnie, D., & Marois, R. (2009). Attentive tracking disrupts feature binding in visual working memory. *Visual Cognition*, *17*(1–2), 48–66. https://doi.org/10.1080/13506280802281337

Goldman-Rakic, P. S. (1988). Topography of Cognition: Parallel Distributed Networks in Primate Association Cortex. *Annual Review of Neuroscience*, *11*(1), 137–156. https://doi.org/10.1146/annurev.ne.11.030188.001033

Gorgoraptis, N., Catalao, R. F. G., Bays, P. M., & Husain, M. (2011). Dynamic Updating of Working Memory Resources for Visual Objects. *Journal of Neuroscience*, *31*(23), 8502–8511.

Gratwicke, J., Jahanshahi, M., & Foltynie, T. (2015). Parkinson ' s disease dementia : a neural networks perspective Executive dysfunction*. Brain, 138*(6)*,* 1454–1476. https://doi.org/10.1093/brain/awv104

Griffin, I. C., & Nobre, A. C. (2003). Orienting attention to locations in internal representations. *Journal of Cognitive Neuroscience*, *15*(8), 1176–1194. https://doi.org/10.1162/089892903322598139

Guzowski, J. F., Knierim, J. J., & Moser, E. I. (2004). Ensemble dynamics of hippocampal regions CA3 and CA1. *Neuron*, *44*(4), 581–584. https://doi.org/10.1016/j.neuron.2004.11.003.

Hay, D. C., Smyth, M. M., Hitch, G. J., & Horton, N. J. (2007). Serial position effects in short-term visual memory: A SIMPLE explanation? *Memory & Cognition*, *35*(1), 176–190.

Heise, V., Filippini, N., Trachtenberg, A. J., Suri, S., Ebmeier, K. P., & Mackay, C. E. (2014). Apolipoprotein E genotype, gender and age modulate connectivity of the hippocampus in healthy adults. *NeuroImage*, *98*, 23–30. https://doi.org/10.1016/j.neuroimage.2014.04.081

Heuer, A., & Schubö, A. (2016). Feature-based and spatial attentional selection in visual working memory. *Memory and Cognition*, *44*(4), 621–632. https://doi.org/10.3758/s13421-015-0584-5

Heuer, A., Schubö, A., & Crawford, J. D. (2016). Different cortical mechanisms for spatial vs. Feature-based attentional selection in visual working memory. *Frontiers in Human Neuroscience*, *10*(8), 1–9. https://doi.org/10.3389/fnhum.2016.00415

Howard, L. R., Javadi, A. H., Yu, Y., Mill, R. D., Morrison, L. C., Knight, R., Loftus, M. M., Staskute, L., & Spiers, H. J. (2014). The hippocampus and entorhinal cortex encode the path and Euclidean distances to goals during navigation. *Current Biology : CB*, *24*(12), 1331–1340. https://doi.org/10.1016/j.cub.2014.05.001

Hu, Y., Allen, R. J., Baddeley, A. D., & Hitch, G. J. (2016). Executive control of stimulus-driven and goal-directed attention in visual working memory. *Atten Percept Psychophys*, *78*, 2164–2175. https://doi.org/10.3758/s13414-016-1106-7

Hu, Y., Hitch, G. J., Baddeley, A. D., Zhang, M., & Allen, R. J. (2014). Executive and perceptual attention play different roles in visual working memory: Evidence from suffix and strategy effects. *Journal of Experimental Psychology: Human Perception and Performance*, *40*(4), 1665–1678. https://doi.org/10.1037/a0037163

Hurlstone, M. J., Hitch, G. J., & Baddeley, A. D. (2014). Memory for serial order across domains: An overview of the literature and directions for future research. *Psychological Bulletin*, *140*(2), 339–373. https://doi.org/10.1037/a0034221

Ihssen, N., Linden, D. E. J., & Shapiro, K. L. (2010). Improving visual short-term memory by sequencing the stimulus array. *Psychonomic Bulletin & Review*, *17*(5), 680–686. https://doi.org/10.3758/PBR.17.5.680

Jacobs, H. I. L., Augustinack, J. C., Schultz, A. P., Hanseeuw, B. J., Locascio, J., Amariglio, R. E., Papp, K. V, Rentz, D. M., Sperling, R. A., & Johnson, K. A. (2020). The presubiculum links incipient amyloid and tau pathology to memory function in older persons. *Neurology*, *94*(18), e1916 LP-e1928. https://doi.org/10.1212/WNL.0000000000009362

Joseph, S., Iverson, P., Manohar, S., Fox, Z., Scott, S. K., & Husain, M. (2015). Precision of working memory for speech sounds. *Quarterly Journal of Experimental Psychology*, *68*(10), 2022–2040. https://doi.org/10.1080/17470218.2014.1002799

Jost, K., Bryck, R. L., Vogel, E. K., & Mayr, U. (2011). Are old adults just like low working memory young adults? Filtering efficiency and age differences in visual working memory. *Cerebral Cortex*, *21*(5), 1147–1154. https://doi.org/10.1093/cercor/bhq185

Kalia, L. V, & Lang, A. E. (2015). Parkinson's disease. *Lancet*, *386*(9996), 896–912. https://doi.org/10.1016/S0140-6736(14)61393-3

Kalm, K., & Norris, D. (2017). NeuroImage A shared representation of order between encoding and recognition in visual short-term memory. *NeuroImage*, *155*(4), 138–146. https://doi.org/10.1016/j.neuroimage.2017.04.047

Kehagia, A. A., Barker, R. A., & Robbins, T. W. (2010). Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. *The Lancet. Neurology*, *9*(12), 1200–1213. https://doi.org/10.1016/S1474-4422(10)70212-X

Kim, C., Kroger, J. K., Calhoun, V. D., & Clark, V. P. (2015). The role of the frontopolar cortex in manipulation of integrated information in working memory. *Neuroscience Letters*, *595*, 25–29. https://doi.org/10.1016/j.neulet.2015.03.044

Kim, S., Sapiurka, M., Clark, R. E., & Squire, L. R. (2013). Contrasting effects on path integration after hippocampal damage in humans and rats. *Proceedings of the National Academy of Sciences*, *110*(12), 4732-4737. https://doi.org/10.1073/pnas.1300869110

King, A., Liu, L., Chuen, R., Chang, C., Pearce, R. K. B., & Gentleman, S. M. (2015). *Nucleus basalis of Meynert revisited : anatomy , history and differential involvement in Alzheimer ' s and Parkinson ' s disease*. 527–540. https://doi.org/10.1007/s00401-015-1392-5

King, J., & Dehaene, S. (2017). *Europe PMC Funders Group Characterizing the dynamics of mental representations : the temporal generalization method*. *18*(4), 203–210. https://doi.org/10.1016/j.tics.2014.01.002.Characterizing

Kirova, A. M., Bays, R. B., & Lagalwar, S. (2015). Working memory and executive function decline across normal aging, mild cognitive impairment, and Alzheimer's disease. *BioMed research international*, *2015*, 748212. https://doi.org/10.1155/2015/748212

Kish, S. J., Tong, J., Hornykiewicz, O., Rajput, A., Chang, L. J., Guttman, M., & Furukawa, Y. (2008). Preferential loss of serotonin markers in caudate versus putamen in Parkinson's disease. *Brain : a journal of neurology*, *131*(Pt 1), 120–131. https://doi.org/10.1093/brain/awm239

Klinkenberg, I., Sambeth, A., & Blokland, A. (2011). Acetylcholine and attention. *Behavioural Brain Research*, *221*(2), 430–442. https://doi.org/10.1016/j.bbr.2010.11.033

Kosslyn, S. M. (1980). *Image and mind*. Harvard University Press .

Kumar, A., Sidhu, J., Goyal, A., & Tsao, J. W. (2021). *Alzheimer Disease.*

Kurth-Nelson, Z., Economides, M., Dolan, R. J., Dayan, P., Kurth-nelson, Z., Economides, M., Dolan, R. J., & Dayan, P. (2016). Fast Sequences of Non-spatial State Representations in Humans Article Fast Sequences of Non-spatial State Representations in Humans. *Neuron*, *91*(1), 194–204. https://doi.org/10.1016/j.neuron.2016.05.028

Landman, R., Spekreijse, H., & Lamme, V. A. F. (2003). Large capacity storage of integrated objects before change blindness. *Vision Research*, *43*(2), 149–164. https://doi.org/10.1016/s0042-6989(02)00402-9

LaRocque, J. J., Lewis-Peacock, J. A., & Postle, B. R. (2014). Multiple neural states of representation in short-term memory? It's a matter of attention. *Frontiers in*

Human Neuroscience, *8*(1), 1–14. https://doi.org/10.3389/fnhum.2014.00005

Lawrence, A. D., & Sahakian, B. J. (1998). The cognitive psychopharmacology of Alzheimer's disease: focus on cholinergic systems. *Neurochemical research*, *23*(5), 787–794. https://doi.org/10.1023/a:1022419712453

Lepsien, J., & Nobre, A. C. (2007). Attentional modulation of object representations in working memory. *Cerebral Cortex*, *17*(9), 2072–2083. https://doi.org/10.1093/cercor/bhl116

Lewis-Peacock, J. A., Drysdale, A. T., Oberauer, K., & Postle, B. R. (2012). Neural evidence for a distinction between short-term memory and the focus of attention. *Journal of Cognitive Neuroscience*, *24*(1), 61–79. https://doi.org/10.1162/jocn_a_00140

Liang, Y., Pertzov, Y., Nicholas, J. M., Henley, S. M. D., Crutch, S., Woodward, F., Leung, K., Fox, N. C., & Husain, M. (2016). Visual short-term memory binding deficit in familial Alzheimer's disease. *Cortex*, *78*, 150–164. https://doi.org/10.1016/j.cortex.2016.01.015

Liu, C.-C., Liu, C.-C., Kanekiyo, T., Xu, H., & Bu, G. (2013). Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nature reviews. Neurology*, *9*(2), 106–118). https://doi.org/10.1038/nrneurol.2012.263

Love, J., Selker, R., Marsman, M., Jamil, T., Dropmann, D., Verhagen, Aj., & Wagenmakers, E. J. (2015). JASP (Version 0.7)[computer software]. *Amsterdam, the Netherlands: Jasp Project*.

Luck, S. J., & Vogel, E. K. (1997). The capacity of visual working memory for features and conjunctions. *Nature*, *390*(6657), 279–281. https://doi.org/10.1038/36846

Mah, Y. H., Husain, M., Rees, G., & Nachev, P. (2014). Human brain lesion-deficit inference remapped. *Brain*, *137*(9), 2522–2531. https://doi.org/10.1093/brain/awu164

Makovski, T., Watson, L. M., Koutstaal, W., & Jiang, Y. V. (2010). Method Matters: Systematic Effects of Testing Procedure on Visual Working Memory Sensitivity. *Journal of Experimental Psychology: Learning Memory and Cognition*, *36*(6), 1466–1479. https://doi.org/10.1037/a0020851

Manohar, S. G., Zokaei, N., Fallon, S. J., Vogels, T. P., & Husain, M. (2019). Neuroscience and Biobehavioral Reviews Neural mechanisms of attending to items in working memory. *Neuroscience and Biobehavioral Reviews*, *101*(1), 1–12. https://doi.org/10.1016/j.neubiorev.2019.03.017

Mathuranath, P. S., Nestor, P. J., Berrios, G. E., Rakowicz, W., & Hodges, J. R. (2000). A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. *Neurology*, *55*(11), 1613–1620. https://doi.org/10.1212/01.wnl.0000434309.85312.19

McElree, B. (2006). Accessing Recent Events, *Academic Press, 46,* 155-200. https://doi.org/https://doi.org/10.1016/S0079-7421(06)46005-9

McElree, B., & Dosher, B. A. (1989). Serial position and set size in short-term memory: The time course of recognition. *Journal of Experimental Psychology: General*, *118*,

4, 346–373. https://doi.org/10.1037/0096-3445.118.4.346

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack Jr, C. R., Kawas, C. H., Klunk, W. E., Koroshetz, W. J., Manly, J. J., Mayeux, R., Mohs, R. C., Morris, J. C., Rossor, M. N., Scheltens, P., Carrillo, M. C., Thies, B., Weintraub, S., & Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association*, *7*(3), 263–269. https://doi.org/10.1016/j.jalz.2011.03.005

Morey, R. D., & Rouder, J. N. (2015). BayesFactor (version 0.9. 10-2). *Computer Software*.

Morgan, L. K., Macevoy, S. P., Aguirre, G. K., & Epstein, R. A. (2011). Distances between real-world locations are represented in the human hippocampus. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *31*(4), 1238–1245. https://doi.org/10.1523/JNEUROSCI.4667-10.2011

Myers, N. E., Stokes, M. G., & Nobre, A. C. (2017). Prioritizing information during working memory: beyond sustained internal attention. *Trends in Cognitive Sciences*, *21*(6), 449–461.

Nee, D. E., & Jonides, J. (2008). Neural correlates of access to short-term memory. *Proceedings of the National Academy of Sciences*, *105*(37), 14228–14233.

Nee, D. E., & Jonides, J. (2011). Dissociable contributions of prefrontal cortex and the hippocampus to short-term memory: evidence for a 3-state model of memory. *Neuroimage*, *54*(2), 1540–1548.

Nee, D. E., & Jonides, J. (2013). Trisecting representational states in short-term memory. *Frontiers in Human Neuroscience*, *7*, 796.

Niklaus, M., Singmann, H., & Oberauer, K. (2019). Two distinct mechanisms of selection in working memory: Additive last-item and retro-cue benefits. *Cognition*, *183*(November 2018), 282–302. https://doi.org/10.1016/j.cognition.2018.11.015

Norman, K. A., & O'Reilly, R. C. (2003). Modeling hippocampal and neocortical contributions to recognition memory: A complementary-learning-systems approach. *Psychological Review*, *110*(4), 611–646. https://doi.org/10.1037/0033-295X.110.4.611

O'Keefe, J., & Nadel, L. (1978). *The Hippocampus as a Cognitive Map*. Oxford: Clarendon Press. http://hdl.handle.net/10150/620894

O'Reilly, R. C., & McClelland, J. L. (1994). Hippocampal conjunctive encoding, storage, and recall: avoiding a trade-off. *Hippocampus*, *4*(6), 661–682. https://doi.org/10.1002/hipo.450040605

Oberauer, K. (2009). Chapter 2 Design for a Working Memory. *Psychology of Learning and Motivation - Advances in Research and Theory*, *51*, 45–100. https://doi.org/10.1016/S0079-7421(09)51002-X

Oberauer, K., & Lin, H.-Y. (2017). An interference model of visual working memory. *Psychological Review*, *124*(1), 21–59. https://doi.org/10.1037/rev0000044 PM - 27869455

Oberauer, K., Stoneking, C., Wabersich, D., & Lin, H.-Y. (2017). Hierarchical Bayesian

measurement models for continuous reproduction of visual features from working memory. *Journal of Vision*, *17*(5), 11. https://doi.org/10.1167/17.5.11

Olivers, C. N. L., Peters, J., Houtkamp, R., & Roelfsema, P. R. (2011). Different states in visual working memory: When it guides attention and when it does not. *Trends in Cognitive Sciences*, *15*(7), 327–334. https://doi.org/10.1016/j.tics.2011.05.004

Osaka, M., Osaka, N., Kondo, H., Morishita, M., Fukuyama, H., Aso, T., & Shibasaki, H. (2003). The neural basis of individual differences in working memory capacity: An fMRI study. *NeuroImage*, *18*(3), 789–797. https://doi.org/10.1016/S1053-8119(02)00032-0

Osth, A. F., & Dennis, S. (2015). The fill-in effect in serial recall can be obscured by omission errors. *Journal of Experimental Psychology: Learning Memory and Cognition*, *41*(5), 1447–1455. https://doi.org/10.1037/xlm0000113

Öztekin, I., Davachi, L., & McElree, B. (2010). Are representations in working memory distinct from representations in long-term memory? Neural evidence in support of a single store. *Psychological Science*, *21*(8), 1123–1133.

Öztekin, I., McElree, B., Staresina, B. P., & Davachi, L. (2009). Working Memory Retrieval: Contributions of the Left Prefrontal Cortex, the Left Posterior Parietal Cortex, and the Hippocampus. *Journal of Cognitive Neuroscience*, *21*(3), 581–593. https://doi.org/10.1162/jocn.2008.21016

Pertzov, Y., Manohar, S., & Husain, M. (2017). Rapid forgetting results from competition over time between items in visual working memory. *Journal of Experimental Psychology: Learning Memory and Cognition*, *43*(4), 528–536. https://doi.org/10.1037/xlm0000328

Pertzov, Y., Miller, T. D., Gorgoraptis, N., Caine, D., Schott, J. M., Butler, C., & Husain, M. (2013). Binding deficits in memory following medial temporal lobe damage in patients with voltage-gated potassium channel complex antibody-associated limbic encephalitis. *Brain*, *136*(8), 2474–2485. https://doi.org/10.1093/brain/awt129

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: clinical characterization and outcome. *Archives of Neurology*, *56*(3), 303–308. https://doi.org/10.1001/archneur.56.3.303

Philbeck, J. W., Behrmann, M., Levy, L., Potolicchio, S. J., & Caputy, A. J. (2004). Path integration deficits during linear locomotion after human medial temporal lobectomy. *Journal of Cognitive Neuroscience*, *16*(4), 510–520. https://doi.org/10.1162/089892904323057254

Pipa, G., Städtler, E. S., Rodriguez, E. F., Waltz, J. A., Muckli, L. F., Singer, W., Goebel, R., & Munk, M. H. J. (2009). Performance- and stimulus-dependent oscillations in monkey prefrontal cortex during short-term memory. *Frontiers in Integrative Neuroscience*, *3*(OCT), 1–13. https://doi.org/10.3389/neuro.07.025.2009

Place, R., Farovik, A., Brockmann, M., & Eichenbaum, H. (2016). Bidirectional prefrontal-hippocampal interactions support context-guided memory. *Nature neuroscience*, *19*(8), 992–994. https://doi.org/10.1038/nn.4327

Postuma, R. B., Berg, D., Stern, M., Poewe, W., Marek, K., & Litvan, I. (2015). *CME MDS Clinical Diagnostic Criteria for Parkinson ' s Disease Centrality of Motor Syndrome — Parkinsonism and PD Criteria Benchmark — The Expert Examination*. *30*(12). https://doi.org/10.1002/mds.26424

Pratte, M. S. (2019). Swap errors in spatial working memory are guesses. *Psychonomic Bulletin and Review*, *26*(3), 958–966. https://doi.org/10.3758/s13423-018-1524-8

Rademaker, R. L., Tredway, C. H., & Tong, F. (2012). Introspective judgments predict the precision and likelihood of successful maintenance of visual working memory. *Journal of Vision*, *12*(13). https://doi.org/10.1167/12.13.21

Raffone, A., & Wolters, G. (2001). A cortical mechanism for binding in visual working memory. *Journal of Cognitive Neuroscience*, *13*(6), 766–785. https://doi.org/10.1162/08989290152541430

Ridley, R. M., Murray, T. K., Johnson, J. A., & Baker, H. F. (1986). Learning impairment following lesion of the basal nucleus of Meynert in the marmoset: Modification by cholinergic drugs. *Brain Research*, *376*(1), 108–116. https://doi.org/https://doi.org/10.1016/0006-8993(86)90904-2

Riegert, C., Galani, R., Heilig, S., Lazarus, C., Cosquer, B., & Cassel, J.-C. (2004). Electrolytic lesions of the ventral subiculum weakly alter spatial memory but potentiate amphetamine-induced locomotion. *Behavioural Brain Research*, *152*(1), 23–34. https://doi.org/https://doi.org/10.1016/j.bbr.2003.09.011

Rolls, E. T. (2013). The mechanisms for pattern completion and pattern separation in the hippocampus. *Frontiers in Systems Neuroscience*, *7*(10), 1–21. https://doi.org/10.3389/fnsys.2013.00074

Rolls, E. T. (2016). Neurobiology of Learning and Memory Pattern separation , completion , and categorisation in the hippocampus and neocortex. *Neurobiology of Learning and Memory*, *129*, 4–28. https://doi.org/10.1016/j.nlm.2015.07.008

Rouder, J. N., Morey, R. D., Speckman, P. L., & Province, J. M. (2012). Default Bayes factors for ANOVA designs. *Journal of Mathematical Psychology*, *56*(5), 356–374.

Roux, F., Wibral, M., Mohr, H. M., Singer, W., & Uhlhaas, P. J. (2012). Gamma-band activity in human prefrontal cortex codes for the number of relevant items maintained in working memory. *Journal of Neuroscience*, *32*(36), 12411–12420. https://doi.org/10.1523/JNEUROSCI.0421-12.2012

Sandberg, A., Tegnér, J., & Lansner, A. (2003). A working memory model based on fast Hebbian learning. *Network: Computation in Neural Systems*, *14*(4), 789–802. https://doi.org/10.1088/0954-898X_14_4_309

Schneegans, S., & Bays, P. M. (2017). Neural architecture for feature binding in visual working memory. *Journal of Neuroscience*, *37*(14), 3913–3925. https://doi.org/10.1523/JNEUROSCI.3493-16.2017

Schumacher, E. H., Cookson, S. L., Smith, D. M., Nguyen, T. V. N., Sultan, Z., Reuben, K. E., & Hazeltine, E. (2018). Dual-task processing with identical stimulus and response sets: Assessing the importance of task representation in dual-task interference. *Frontiers in Psychology*, *9*(JUN), 1–7. https://doi.org/10.3389/fpsyg.2018.01031

Schurgin, M. W., Wixted, J. T., & Brady, T. F. (2020). Psychophysical scaling reveals a

unified theory of visual memory strength. *Nature Human Behaviour*. https://doi.org/10.1038/s41562-020-00938-0

SCOVILLE, W. B., & MILNER, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of neurology, neurosurgery, and psychiatry*, *20*(1), 11–21. https://doi.org/10.1136/jnnp.20.1.11

Shallice, T., & Warrington, E. K. (1970). Independent functioning of verbal memory stores: a neuropsychological study. *The Quarterly Journal of Experimental Psychology*, *22*(2), 261–273. https://doi.org/10.1080/00335557043000203

Shallice, Timothy, Burgess, P., Robertson, I., Roberts, A. C., Robbins, T. W., & Weiskrantz, L. (1996). The domain of supervisory processes and temporal organization of behaviour. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, *351*(1346), 1405–1412. https://doi.org/10.1098/rstb.1996.0124

Silver, M. A., Shenhav, A., & D'Esposito, M. (2008). Cholinergic enhancement reduces spatial spread of visual responses in human early visual cortex. *Neuron*, *60*(5), 904–914. https://doi.org/10.1016/j.neuron.2008.09.038

Singer, W. (2009). Distributed processing and temporal codes in neuronal networks. *Cognitive Neurodynamics*, *3*(3), 189–196. https://doi.org/10.1007/s11571-009-9087-z

Smith, E. E., & Jonides, J. (1998). Neuroimaging analyses of human working memory. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(20), 12061–12068. https://doi.org/10.1073/pnas.95.20.12061

Solway, A., Murdock, B. B., & Kahana, M. J. (2012). *Positional and temporal clustering in serial order memory*. *11*, 177–190. https://doi.org/10.3758/s13421-011-0142-8

Song, D., Wang, D., Yang, Q., Yan, T., Wang, Z., Yan, Y., Zhao, J., Xie, Z., Liu, Y., Ke, Z., Qazi, T. J., Li, Y., Wu, Y., Shi, Q., Lang, Y., Zhang, H., Huang, T., Wang, C., Quan, Z., & Qing, H. (2020). The lateralization of left hippocampal CA3 during the retrieval of spatial working memory. *Nature Communications*, *11*(1), 2901. https://doi.org/10.1038/s41467-020-16698-4

Souza, A. S., & Oberauer, K. (2016). In search of the focus of attention in working memory: 13 years of the retro-cue effect. *Attention, Perception, and Psychophysics*, *78*(7), 1839–1860. https://doi.org/10.3758/s13414-016-1108-5

Souza, A. S., Rerko, L., & Oberauer, K. (2014). Unloading and reloading working memory: Attending to one item frees capacity. *Journal of Experimental Psychology: Human Perception and Performance 40*(3), 1237–1256. https://doi.org/10.1037/a0036331

Souza, A. S., Rerko, L., & Oberauer, K. (2016). Getting more from visual working memory: Retro-cues enhance retrieval and protect from visual interference. *Journal of Experimental Psychology: Human Perception and Performance*, *42*(6), 890.

Sperling, G. (1960). The information available in brief visual presentations. *Psychological Monographs: General and Applied*, *74*(11), 1.

Stokes, M. G., Kusunoki, M., Sigala, N., Nili, H., Gaffan, D., & Duncan, J. (2013). Dynamic

coding for cognitive control in prefrontal cortex. *Neuron*, *78*(2), 364–375. https://doi.org/10.1016/j.neuron.2013.01.039

Tabi, Y. A., Husain, M., & Manohar, S. G. (2019). Recall cues interfere with retrieval from visuospatial working memory. *British journal of psychology (London, England : 1953)*, *110*(2), 288–305. https://doi.org/10.1111/bjop.12374

Tabi, Y. A., Maio, M. R., Fallon, S. J., Udale, R., Dickson, S., Imran, M., Nobis, L., Manohar, S. G., & Husain, M. (2021). Impact of processing demands at encoding , maintenance and retrieval in visual working memory. *Cognition*, *214*, 104758. https://doi.org/10.1016/j.cognition.2021.104758

Toniolo, S., Maio, M. R., Tabi, Y. A., Slavkova, E., Plant, O., Saleh, Y., Attaallah, B., Idris, I., Peixoto, J., Preul, C., Srowig, A., Joedecke, S., Butler, C., Thompson, S., Manohar, S., Finke, K., & Husain, M. (2020). A novel visual short-term memory task differentiates MCI and Alzheimer's patients from healthy ageing. *Alzheimer's & Dementia*, *16*(S6), e043006. https://doi.org/https://doi.org/10.1002/alz.043006

Upton, J. (2013). Mini-Mental State Examination. In M. D. Gellman & J. R. Turner (Eds.), *Encyclopedia of Behavioral Medicine*, 1248–1249. Springer New York. https://doi.org/10.1007/978-1-4419-1005-9_473

Vago, D. R., & Kesner, R. P. (2008). Disruption of the direct perforant path input to the CA1 subregion of the dorsal hippocampus interferes with spatial working memory and novelty detection. *Behavioural Brain Research*, *189*(2), 273–283. https://doi.org/10.1016/j.bbr.2008.01.002

van Moorselaar, D., Gunseli, E., Theeuwes, J., & Olivers, C. N. L. (2015). The time course of protecting a visual memory representation from perceptual interference. *Frontiers in Human Neuroscience*, *8*(1), 1–9. https://doi.org/10.3389/fnhum.2014.01053

van Moorselaar, D., Olivers, C. N. L., Theeuwes, J., Lamme, V. A. F., & Sligte, I. G. (2015). Forgotten but not gone: Retro-cue costs and benefits in a double-cueing paradigm suggest multiple states in visual short-term memory. In *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *41*(6), 1755–1763). https://doi.org/10.1037/xlm0000124

Verbaan, D., Marinus, J., Visser, M., Rooden, S. M. Van, Stiggelbout, A. M., Middelkoop, H. A. M., & Hilten, J. J. Van. (2007). *Cognitive impairment in Parkinson ' s disease*. 1182–1187. https://doi.org/10.1136/jnnp.2006.112367

Vogel, E. K., McCollough, A. W., & Machizawa, M. G. (2005). Neural measures reveal individual differences in controlling access to working memory. *Nature*, *438*(7067), 500–503. https://doi.org/10.1038/nature04171

Wang, Y., Roth, Z., & Pastalkova, E. (2016). Synchronized excitability in a network enables generation of internal neuronal sequences. *eLife*, *5*, e20697. https://doi.org/10.7554/eLife.20697

Wesnes, K. A., McKeith, I., Edgar, C., Emre, M., & Lane, R. (2005). Benefits of rivastigmine on attention in dementia associated with Parkinson disease. *Neurology*, *65*(10), 1654 – 1656. https://doi.org/10.1212/01.wnl.0000184517.69816.e9

Wheeler, M. E., & Treisman, A. M. (2002). Binding in Short-Term Visual Memory. *Smith*

& Jonides, *131*, 48–64. https://doi.org/10.1037//0096-3445.131.1.48

Williams, M., Hong, S. W., Kang, M. S., Carlisle, N. B., & Woodman, G. F. (2013). The benefit of forgetting. *Psychonomic Bulletin and Review*, *20*(2), 348–355. https://doi.org/10.3758/s13423-012-0354-3

Wolff, M. J., Jochim, J., Akyürek, E. G., & Stokes, M. G. (2017). *Europe PMC Funders Group Dynamic hidden states underlying working memory guided behaviour*. *20*(6), 864–871. https://doi.org/10.1038/nn.4546.Dynamic

Worsley, C. L., Recce, M., Spiers, H. J., Marley, J., Polkey, C. E., & Morris, R. G. (2001). Path integration following temporal lobectomy in humans. *Neuropsychologia*, *39*(5), 452–464. https://doi.org/10.1016/s0028-3932(00)00140-8

Yu, A., & Dayan, P. (2002). Expected and Unexpected Uncertainty: ACh and NE in the Neocortex. In *Adv. Neural Inf. Proc. Syst.* (Vol. 15).

Yu, X., Chen, Y., Qiu, J., Li, X., & Huang, X. (2017). Neural oscillations associated with auditory duration maintenance in working memory. *Scientific Reports*, *7*(1), 1–9. https://doi.org/10.1038/s41598-017-06078-2

Zarow, C., Lyness, S. A., Mortimer, J. A., & Chui, H. C. (2003). Neuronal Loss Is Greater in the Locus Coeruleus Than Nucleus Basalis and Substantia Nigra in Alzheimer and Parkinson Diseases. *Archives of Neurology*, *60*(3), 337–341. https://doi.org/10.1001/archneur.60.3.337

Zhang, W., & Luck, S. J. (2008). Discrete fixed-resolution representations in visual working memory. *Nature*, *453*(7192), 233–235. https://doi.org/10.1038/nature06860

Zokaei, N., Giehl, K., Sillence, A., Neville, M. J., Karpe, F., Nobre, A. C., & Husain, M. (2017). Sex and APOE: A memory advantage in male APOE ε4 carriers in midlife. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *88*, 98–105. https://doi.org/10.1016/j.cortex.2016.12.016

Zokaei, N., Gorgoraptis, N., Bahrami, B., Bays, P. M., & Husain, M. (2011). Precision of working memory for visual motion sequences and transparent motion surfaces. *Journal of Vision*, *11*(14), 1–18. https://doi.org/10.1167/11.14.2

Zokaei, N., Heider, M., & Husain, M. (2014). Attention is required for maintenance of feature binding in visual working memory. *Quarterly Journal of Experimental Psychology*, *67*(6), 1191–1213. https://doi.org/10.1080/17470218.2013.852232

Zokaei, N., & Husain, M. (2019). *Working Memory in Alzheimer's Disease and Parkinson's Disease BT - Processes of Visuospatial Attention and Working Memory* (T. Hodgson (Ed.); pp. 325–344). Springer International Publishing. https://doi.org/10.1007/7854_2019_103

Zokaei, N., Manohar, S., Husain, M., & Feredoes, E. (2014). Causal evidence for a privileged working memory state in early visual cortex. *Journal of Neuroscience*, *34*(1), 158–162. https://doi.org/10.1523/JNEUROSCI.2899-13.2014

Zokaei, N., Ning, S., Manohar, S., Feredoes, E., & Husain, M. (2014a). Flexibility of representational states in working memory. *Frontiers in Human Neuroscience*, *8*,

853. https://doi.org/10.3389/fnhum.2014.00853

Zokaei, N., Sillence, A., Kienast, A., Drew, D., Plant, O., Slavkova, E., Manohar, S. G., & Husain, M. (2020). ScienceDirect Different patterns of short-term memory deficit in Alzheimer ' s disease , Parkinson ' s disease and subjective cognitive impairment. *CORTEX*, *132*, 41–50. https://doi.org/10.1016/j.cortex.2020.06.016