Memory transience versus memory persistence

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Publication date
2022

CHAPTER 1

General introduction

Forgetting is a phenomenon we both loathe and love. Almost without exception we take pictures of precious events in our lives (e.g., weddings, graduations, births). This illustrates that without memory aids we sometimes struggle to retrieve our most valuable memories, and that habits to counteract forgetting can become anchored in culture. Our desire to retain more events in memory than we are capable of is also reflected in popular music. The experiences and frustrations that accompany the searching of memory have been a source of inspiration for many artists (e.g., Robert Plant: "I am a traveler of both time and space, to be where I have been"[1]; Eddie Vedder: "I cannot find the candle of thought to light your name"). At the same time, forgetting can be very helpful when we need to overcome adversity (e.g., moving on after a painful break-up). Moreover, since we store an extremely large amount of information in the brain, forgetting is not only desired under sad circumstances, but a general requirement to thrive in our environment. If we remembered everything we once knew, we would become overloaded with details and fail at the ultimate purpose for which we rely on memory: having the right information available at the right time (Roediger et al., 2010).

The need to forget is illustrated by a case description showing what problems can occur when someone possesses what many would describe as an almost perfect memory (Parker et al., 2006). In 2000, a woman sought help from James L. McGaugh (a pioneer in the science of learning and memory) for a highly unusual memory problem. She described that her memory of personally experienced events was so extensive and powerful that she would often be overwhelmed by her own recollections of the past. In short, the triggering of one detailed memory led to the triggering of another and another, resulting in an endless, uncontrollable, and exhausting stream of associations. Dr. McGaugh and colleagues, both curious and skeptical about the story, met with this woman and performed memory tests over the course of several years to gain insight into her mnemonic abilities. They found that even though most of her abilities were average and some even below average, she could recall personally experienced events extremely well, most notably in relation to dates. One could for example mention a random date, years ago from today, and she would retrieve the day of the week (e.g., Wednesday) and many details of what happened during that day with ease. She was extremely consistent and nearly perfectly accurate, as shown by a diary she had kept from the age of 10 to 34 and news facts over several decades. Neuropsychological testing also revealed that she had an exceptional ability to form what is termed episodic memory (i.e., memories that include remembering what happened during an event, where it happened, and when, leading to a recollective experience during recall, Tulving, 2002). The authors proposed that her abilities could perhaps be traced back to a rather obsessive tendency to memorize what had happened on every day in a highly structured manner. It seemed that this woman had gotten so good at this, she now had to face

1 Interestingly, as elegantly pointed out by Ekstrom and Ranganath (2018), Robert Plant in this line specifies the defining feature of episodic memories: Recollection of an event's time and place.

consequences not even an experienced memory researcher could have had foreseen: regular bothersome intruding of irrelevant memories of past events.

Although convincing evidence for disruptive effects of "too little forgetting" is limited by the rarity of such problems and the few possibilities to firmly fact-check someone's past, this case exemplifies how at present the functional nature of memory is viewed. The most effective memory system is not analogous to a storehouse that contains as much information as possible. It is the *flexibility* of memory that is key for optimal adaption to one's environment. In other words, rather than retaining as many events as possible in as much detail is possible, having the crucial pieces of information available that one particularly needs at the right moment is where the challenge lies (Roediger et al., 2010). For this purpose, the selection of the most valuable pieces of information during learning is essential, but also the updating of one's memory. Our environments change regularly and therefore our memory should be adapted accordingly. If this would not happen, all we could rely on are outdated representations of the past and we would be poorly equipped to deal with future challenges. For these reasons, it is not surprising that flexible changes of memory are very topical in psychological science and neuroscience. Many decades of research have already provided highly important insights into how memories transform: from being lost, to being strengthened, to being distorted. At the same time, a detailed understanding of how memories change is far from achieved, as a multitude of key questions remain unresolved. The present dissertation aims to unravel parts of the dynamic nature of memory and focuses on several classic factors in particular.

1. Time and spatial context

Perhaps the most well-known change in memory is its natural development over time. A very recent memory that can be retrieved vividly and in much detail today is often reduced, stripped of its rich details, at a later time. Research shows that during this process of decay, the central element of an event (e.g., the person one was interacting with) is retained to a larger degree than more peripheral aspects of the event (e.g., Cox et al., 2014; Sekeres et al., 2016; Talamini & Gorree, 2012). Memory thus undergoes a transformation with time, becoming increasingly more gist-like. Neurobiologically, memory is thought to be initially mediated by representations in the hippocampus, a brain region that is crucial for episodic memory (Burgess et al., 2002). With the passage of days, weeks, or years, the memory gradually becomes more dependent on the neocortex, a brain region that mediates fact-like knowledge (i.e., semantic memory, Barry & Maguire, 2019; Frankland & Bontempi, 2005; Meeter & Murre, 2004; Moscovitch et al., 2016; Tonegawa et al., 2018). This so-called schematization of memory is believed to be functional by enabling abstraction or generalization of knowledge, which can be applied in a wide range of new situations.

Since it is useful to preferentially remember those pieces of information that will likely be valuable in the future, it is not surprising that some events have an exceptional status in the process of memory decay: emotional experiences. These are events that are of most personal significance and, therefore, crucial to preserve. Indeed, a wealth of research shows that emotional material both draws more attention than neutral material (i.e., enters memory more often), and is retained to a larger degree (i.e., stays in memory more often, Hamann, 2001). However, recent studies suggest that not all aspects of emotional events are strengthened relative to neutral events. It seems that even though emotional items are well retained, the more peripheral aspects (such as the spatial context in which the event took place) are not enhanced or even impaired in memory (Bisby & Burgess, 2014; Kensinger, 2009; Kensinger et al., 2007; Matsumoto & Kawaguchi, 2020; van Ast et al., 2013, 2014; Yonelinas & Ritchey, 2015). One of the frequently mentioned explanations for this effect, the narrowing-of-attention hypothesis, posits that increased attention drawn by threatening features of an event (i.e., emotional items) is consequently shifted away from the less relevant, peripheral details (Easterbrook, 1959; Kensinger et al., 2007; Loftus et al., 1987). As a result, strong item memory and weak contextual memory is formed (see Kensinger 2009 for a review of the empirical evidence).

Although privileged remembering of particularly important information (i.e., emotional items) is generally an adaptive mechanism, it sometimes comes at a cost. Approximately 30% of the population at some point in life meets the diagnostic criteria of an anxiety disorder or posttraumatic stress disorder (PTSD) (Kessler et al., 2005, 2012), which are characterized by excessive emotional memories (Kindt, 2014). It is believed that enhanced memory for central emotional elements, together with reduced contextual memory may play an important role in the aetiology of such disorders (Maren et al., 2013). It is well-established that retrieval of memory is usually much stronger when one returns to the spatial context in which an event took place, compared to a context that is unrelated to the learning event (Godden & Baddeley, 1975; Smith, 1979). In fact, spatial context is regarded as a primary determinant of memory accessibility and together with time constitutes the hallmark of episodic memory (Tulving, 2002). However, due to its strong item but weak context representations, contextual dependency of memory is lower for emotional than neutral events (van Ast et al., 2013, 2014). Consequently, emotional memory could become prone to reactivation in safe situations, which is manifested in symptoms that typify anxiety disorders and PTSD (e.g., fear generalization and memory intrusions). In this way, emotional memories may develop such that a pathological manifestation of fear emerges (Acheson et al., 2012; Brewin et al., 2010; Ehlers & Clark, 2000; Lambert & McLaughlin, 2019; Liberzon & Abelson, 2016).

Nevertheless, thorough insights into the decay of human emotional memory components are lacking so far. In previous studies, memory testing was mostly performed relatively quick after learning and limited to one time point (e.g., on the same day or one day later, Bisby & Burgess, 2014; Kensinger, 2009; Kensinger et al., 2007; Matsumoto & Kawaguchi, 2020; van Ast et al., 2013, 2014; Yonelinas & Ritchey, 2015). Thus, whether emotional memories are truly characterized by strengthened item and weakened contextual dependency at the long term is unclear. Assuming that they are, the development of treatments that specifically target the reduced contextual dependency of emotional memory may be important. Current treatments are usually focused on “emotional hotspots” and do not necessarily deal with contextual dependency of memory (de Voogd et al., 2018; Holmes et al., 2005; Mineka & Oehlberg, 2008). Provided that emotional memories are indeed characterized by low contextual dependency and that this poses a problem for patients, strategies to bolster contextual dependency of memory may be useful to complement existing interventions.

In short, time and spatial context are crucial factors in the flexible nature of memory, by enabling access to the right information at the right moment. It seems that some of the involved processes (e.g., preferential remembering of emotional aspects of an event) sometimes operate to such a powerful extent that excessive emotional memories arise. Gaining more detailed insights into these mechanisms may help to better understand the development of dysfunctional memory and to optimize treatments that effectively target its roots.

2. Interference

Another well-known influence on memory retrieval is interference from new learning events. Müller and Pilzecker (some of the founding fathers of experimental psychology) performed the first study into this phenomenon in 1900 (Lechner et al., 1999; Müller & Pilzecker, 1900). They presented participants (often their spouses or themselves) with a list of nonsense syllable pairs to study. A second list of pairs was studied afterwards or no further studying took place. Then, memory of the first list was tested by presenting the first syllable of each pair as a cue. The result showed that cued recall performance was worse when learning of the second list had taken place, compared to when no interpolated learning was performed. Based on a total of 40 of such experiments involving paired associates learning, the authors eventually concluded that memories are prone to interference from new learning events, particularly those that occur in close temporal proximity to the original learning. This seminal study marked the beginning of the interference era (Anderson, 2003), during which retroactive memory effects (influences from new events on existing memory), but also proactive ones (influences from existing memory on new learning), were extensively studied. One of the most central claims that originated from this research is that interference is most likely to occur when learning events are somehow similar (e.g., when paired associates belonging to two lists contain the same cue syllable, McGeoch, 1932). At present, there remains little doubt that interference between overlapping memories can indeed be a cause of forgetting.

However, somewhat more recent research shows that memory overlap does not necessarily lead to interference. The occurrence of a new overlapping event can trigger retrieval of the original memory, which in fact can have enhancing – instead of impairing effects – on later recall (Chanales et al., 2019; Jacoby & Wahlheim, 2013; Schlichting & Preston, 2014; Szpunar et al., 2008; Wahlheim, 2015). Interestingly, in modern research, paired associates learning is employed to study both of these phenomena (e.g., Ellenbogen et al., 2006; Schlichting & Preston, 2014), even though it is not understood when one (i.e., interference) or the other (i.e., enhancement) occurs. Thus, despite that decades of research show that similar memories can interfere with each other, it seems that there are currently unknown factors at play which modulate whether overlapping memories indeed impair - or rather facilitate – memory performance.

Germane to the previous discussion on memory decay, emotional events seem to be a special case for interference by new learning. Indeed, emotional memories are much more difficult to interfere with than neutral memories. This resistance to change that typifies emotional memory is a huge challenge in clinical psychology (Kindt, 2014). In exposure-based interventions (the current gold standard to treat anxiety disorders) patients are confronted with situation(s) they fear (e.g., public speaking in case of a social phobia). Consequently, a memory is formed that includes new information (e.g., public speaking is no dangerous activity) that interferes with the fear memory (e.g., public speaking is highly threatening, Bouton, 2002). Although usually experiencing a short-term alleviation, many patients encounter relapse after such exposure-based interventions (Vervliet et al., 2013), which illustrates the tenacity of emotional memories and poses a problem for effective treatment.

Fear-conditioning experiments in the laboratory shed light on the exact mechanisms underlying this prevalent return of fear. In this research paradigm, participants are commonly presented with two visual stimuli on a computer screen, of which one is sometimes followed by a mild electrical stimulus administered to the wrist. This leads to the formation of a fear memory, involving an association between the conditioned stimulus (CS, visual stimulus) and the unconditioned stimulus (US, electrical stimulus). After sufficient pairing of these two stimuli, a conditioned response (CR, fear) develops when presented with the CS alone. When this creation of a fear memory is followed up by repeated presentation of the CS without occurrence of the US (extinction training, the experimental analogy of exposure treatment), the fear response is initially extinguished. However, fear responding resurfaces when the CS is presented in a different context than during learning (renewal), the US is presented without occurrence of the CS (reinstatement), or simply time has passed (spontaneous recovery, Bouton, 2002). These mechanisms thus show that extinction training does not cure fear but merely offers a temporary solution, providing an explanation for the frequent relapse seen in clinical practice (Vervliet et al., 2013).

In sum, apart from time and spatial context, the occurrence of a new event that resembles an event stored in memory is an important determinant of memory accessibility. It remains unclear however when similar memories interfere with each other or rather facilitate later recall. Furthermore, since interference with aversive memories by extinction training often leads to a merely transient reduction of fear, it seems important to develop ways through which a more permanent change in emotional memory can be achieved.

3. Reconsolidation

Interestingly, neuroscientific developments point at a new way of targeting emotional memory through which relapse after treatment may be avoided. In 2000, it was rediscovered that memories can become subject to change upon their reactivation. Using an animal fear-conditioning paradigm, researchers observed that infusing a protein synthesis inhibitor (anisomycin) into the amygdala after exposure to a CS (a tone that was previously paired with a shock, i.e., the US) reduces freezing behavior 24 hours later (Nader et al., 2000). Such reductions in fear responding were not found (or to a lesser degree) in animals that received a placebo solution after exposure to the CS or were infused with anisomycin in the absence of exposure to the CS. These researchers thus demonstrated that the combination of memory reactivation and protein synthesis blockade neutralized fear responding. Importantly, this reactivation-dependent reduction in freezing was later shown to be more durable than the effects of extinction training (e.g., Debiec et al., 2002; Dębiec and Ledoux, 2004; Duvarci, 2004; Bustos et al., 2006, but see e.g., Eisenberg and Dudai, 2004; Lattal and Abel, 2004). As these findings resemble the labile phase that memories go through after initial learning (i.e., consolidation), this process was referred to as reconsolidation (Sara, 2000). Apart from purely theoretical considerations about the plasticity of memory, these studies sparked ideas about relevant clinical applications. If the emotional component of human fear memories can be disposed of, a powerful intervention for anxiety disorders and PTSD could perhaps be realized. However, studies involving experimental animals that learn an association between a tone and a shock do not perfectly reflect the complexity of fears and anxiety disorders in clinical practice.

Since the study of Nader et al. (2000), translational research has brought these findings a step closer to a treatment that is suitable for application in the clinic. It was shown that propranolol (a beta-adrenergic receptor antagonist), which unlike anisomycin is safe for use in humans, can interfere with reactivated fear memories as well (Dębiec & Ledoux, 2004). Subsequently, a successful translation to conditioned fear in humans was performed. In a series of studies it was found that oral administration of propranolol, combined with fear memory reactivation, reduces fear responding while leaving declarative knowledge (i.e., awareness of which stimulus was followed by a US during conditioning) unaffected (Kindt & Soeter, 2018; Kindt, Soeter, & Vervliet, 2009; Sevenster, Beckers, & Kindt, 2012, 2013, 2014; Soeter & Kindt, 2010, 2011, 2012b, 2012a, 2015b, but see Bos et al., 2014; Schroyens et al., 2017; Chalkia et al., 2019). These fear reductions withstood tests for renewal (Soeter & Kindt, 2012a), reinstatement (e.g., Kindt et al., 2009), and spontaneous recovery (Soeter & Kindt, 2010). Another important step was taken when it became apparent that subclinical fear of spiders (i.e., developed outside the laboratory) can be treated by administration of propranolol after a short memory reactivation (Soeter & Kindt, 2015a). Therefore, based on this research a highly effective way of interfering with emotional memories may be within reach.

However, the conditions that are necessary to induce reconsolidation are much more complex than they may initially seem. For instance, it has been shown that mere retrieval of a fear memory is not sufficient for it to become sensitive to modification. Only when exposure to the CS during reactivation has an outcome that is unexpected based on the original conditioning experience (e.g., less aversive due to the absence of the US) can amnestic drugs like propranolol induce a reduction in fear responding (Lee, 2009; Pedreira et al., 2004; Sevenster et al., 2012). Also, several boundary conditions of memory reconsolidation have been identified. Stronger fear memories (i.e., those that have been acquired with a higher intensity US or more frequent USs) and older fear memories are usually less sensitive to procedures aimed at disrupting memory reconsolidation (Bustos et al., 2009; Suzuki et al., 2004; Wang et al., 2009). Although these apparent boundary conditions of reconsolidation are not necessarily unconquerable, they do complicate translation to clinical practice where therapists attempt to target fear memories of varying strengths and ages (Elsey & Kindt, 2017). For a reconsolidation-based intervention to work consistently, insights into how the treatment procedure can be adjusted to overcome the general persistence of stronger and older fear memories is needed.

Ultimately, these issues underscore that the apparent ease through which memory can be changed is highly misleading. Not surprisingly, deciphering the conditions that drive the fate of memory upon its reactivation has been described as on the of the most fundamental questions in the field of memory today (Ritvo et al., 2019). Experiments aimed at elucidating how potential boundary conditions of reconsolidation may be circumvented can contribute to overcoming this challenge.

4. Aim and outline of the dissertation

In the work presented in this thesis, I aimed to further delve into the roles of time, spatial context, interference, and reconsolidation in the flexible nature of memory, to advance our understanding of these processes and eventually provide a basis for useful applications. This aim is somewhat different from the initial objective of my thesis. Originally, we planned to study in a human fear-conditioning paradigm how a reconsolidation intervention may be optimized to treat patients with fear memories of different strengths and ages. We also planned to perform a clinical study in which we intended to apply the insights from such fundamental research, as patient studies so far have yielded mixed results (Brunet et al., 2008, 2011, 2018; Elsey et al., 2020; Kindt & van Emmerik, 2016; Roullet et al., 2021; Wood et al., 2015). However, I faced several challenges when setting up and conducting this envisioned research. First, creating a robust human fear memory (let alone multiple ones of different strengths) proved to be more difficult than anticipated. Also, government measures in response to the COVID-19 outbreak prevented the continuation and eventual completion of the clinical study.

For these reasons, we came up with alternative approaches to gain important insights into the dynamic nature of memory. We employed different experimental paradigms and studied changeability of memory more broadly, from its natural development over time (**Chapter 2**), to manipulations of contextual dependency (**Chapter 3**), determinants of interference versus enhancement (**Chapter 4**), and boundary conditions of memory reconsolidation (**Chapter 5**). To study reconsolidation, I switched from human to animal fear-conditioning research. This enabled us to flexibly induce memories of different strengths, in line with our aim to study boundary conditions of this process. The switch to animal models also fit my personal desire to gain valuable experience with the starting point of translational research (i.e., preclinical work). In the other studies included in this dissertation, we employed well-established paradigms to study changes in episodic memory. I used a classic paired associates procedure (**Chapter 4**) and built on previously developed methods (Cox et al., 2014; van Ast et al., 2013, 2014) to study changes in contextual dependency of memory (**Chapter 2 and 3).**

Specifically, **Chapter 2** was based on the observation that surprisingly little is known about how subcomponents of emotional memory (item and contextual dependency) develop over time. As described earlier, the strength of these components may ultimately pose a vulnerability for the development of fear generalization and intrusions. Therefore, to gain a better understanding of how emotional memories are characterized (and perhaps should be targeted), we conducted a large-scale study in which changes in item memory and contextual dependency of emotional and neutral memories over time were compared.

Chapter 3 is a study in which a novel promising approach to promote contextual dependency of emotional memory was tested. Animal research has shown that fear generalization can be weakened by reexposure to the context in which fear conditioning took place (Al Abed et al., 2020; de Oliveira Alvares et al., 2012; Sekeres et al., 2020; Sevenster et al., 2017, 2018; Wiltgen & Silva, 2007; Winocur et al., 2009; Zhou & Riccio, 1994). Since exposure to a context that resembles the conditioning environment leads to enhanced fear generalization (de Oliveira Alvares et al., 2012; Fujinaka et al., 2016), it seems that a return to the exact same context as during learning is imperative for this therapeutic "recontextualization" of memory. We tested whether these findings could be translated to contextual dependency of human emotional memory. We predicted that reexposure to the encoding context improves, but exposure to a similar context impairs, contextual dependency of episodic memory.

In the study we report in **Chapter 4,** we aimed to uncover when similar episodic memories interfere with each other or enhance memory recall. Specifically, using a paired associates paradigm we tested if the spatial context in which learning takes place determines whether impairment or enhancement of memory occurs. Since paired associates learning has been used to study both memory interference and facilitation, the current state of the literature is somewhat paradoxical (i.e., memory overlap apparently can have two opposite consequences). We tested whether a modulating role of spatial context could solve this paradox.

Finally, **Chapter 5**, was concerned with the malleability of conditioned fear responses by reconsolidation. We conducted a series of 12 experiments of which the aim was twofold. First, by systematically varying fear-conditioning procedures (e.g., the intensity and number of the USs), we aimed to gain more insights into boundary conditions of reconsolidation and how these may be overcome. Second, we attempted to improve understanding of the neurobiological ways through which propranolol influences reconsolidation of contextual fear memories, which so far is not well described. To be certain that we blocked protein synthesis sufficiently, we not only included conditions in which propranolol was administered, but also used the powerful protein synthesis inhibitor anisomycin (like Nader et al. (2000) used in their classic paper described earlier). We additionally included a molecular marker of reconsolidation (Bhattacharya et al., 2017; Rao-Ruiz et al., 2011) to verify whether we actually triggered this mechanism. Finally, in **Chapter 6**, I summarize the studies included in my dissertation and discuss their individual and shared contributions to the understanding of the dynamic nature of memory.