Memory transience versus memory persistence

Cox, W.R.

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CHAPTER 6

General discussion

To thrive in the ever-changing environment we live in, our memory needs to be updated regularly. Indeed, if memory would be static – instead of dynamic - we would be poorly equipped to deal with future challenges. Time, spatial context, interference, and reconsolidation have been recognized as important factors and processes in this flexible nature of memory. However, even though research performed over more than a century provides many insights into the roles of these determinants of memory change, important questions remain unresolved. In the first chapters of this dissertation (**Chapter 2-4**), a human episodic memory paradigm was employed to address several key issues. We studied how memories may transform over time (**Chapter 2**), tested a novel approach to bolster contextual dependency of memory (**Chapter 3**), and assessed how contextual similarity across events modulates memory accessibility (**Chapter 4**). Some of this work (i.e., particularly **Chapter 2 and 3**) was carried out to increase fundamental understanding of changes in emotional memories, which are believed to lie at the root of affective disorders. In the final study described in this dissertation (**Chapter 5**), we used an animal fear-conditioning paradigm to uncover how potential boundary conditions of fear memory reconsolidation may be overcome. These experiments were carried out to inform translational attempts that are aimed at bringing a revolutionary reconsolidation-based intervention to the clinic. In the general discussion, I will summarize the main outcomes of each individual study, synthesize insights across these studies, highlight several outstanding questions, and discuss the major takeaways for translational efforts.

1. Summary of studies

In **Chapter 2**, a study is reported in which the time-dependent trajectories of emotional and neutral episodic memory components were compared. In similar previous research, memory tests were limited to single time points that were scheduled quickly after learning (Sharot & Phelps, 2004; Sharot & Yonelinas, 2008). Also, several studies suffered from methodological limitations, such as low power, suboptimal analytic strategies, or designs that pose problems in the interpretation of the data (e.g., repeated testing of learned material) (Ritchey et al., 2008; Wang, 2014, 2018; Wang & Fu, 2011; Weymar et al., 2011). We therefore performed an experiment specifically aimed at overcoming these shortcomings to better characterize the decay of emotional episodic memories. We hypothesized that emotional memories, compared to neutral memories, would, with the passage of time, become increasingly characterized by relatively strong item memory but weak contextual dependency. In a large-scale study, we indeed found support for this idea. Although contextual dependency surprisingly grew larger – not smaller – with time, emotional item memory became increasingly stronger and contextual dependency increasingly weaker for emotional versus neutral memories. These findings therefore extend previous studies in which similar changes in memory were observed during tests performed only shortly after learning. Furthermore, our observations suggest that differences in the decay of subcomponents of emotional versus neutral memories may become even stronger with additional passage of time.

Given the reduced contextual dependency of emotional memory as demonstrated in **Chapter 2** (and in previous research, e.g., van Ast et al., 2013, 2014), it seems relevant to study how emotional memory activation can be restricted to the context in which original learning took place. According to influential clinical models, poor contextual binding of emotional events may be expressed in fear generalization and memory intrusions, which are symptoms of anxiety disorders and PTSD (Acheson et al., 2012; Brewin et al., 2010; Ehlers & Clark, 2000; Lambert & McLaughlin, 2019; Liberzon & Abelson, 2016). Preclinical work has shown that reexposure to the context in which an emotional event has occurred is a promising approach to reduce fear generalization (Al Abed et al., 2020; de Oliveira Alvares et al., 2012; Sekeres et al., 2020; Wiltgen & Silva, 2007; Winocur et al., 2009; Zhou & Riccio, 1994). These findings have however not been translated to contextual dependency of human episodic memory, which was one of the aims of **Chapter 3.** In this study, we also tested whether exposure to a context that resembles – but is not identical to – the encoding context poses a risk when one attempts to increase contextual dependency of memory (de Oliveira Alvares et al., 2012; Fujinaka et al., 2016). We reasoned that reexposure to the encoding context should trigger memory integration of forgotten aspects of this context into the original memory, such that contextual dependency becomes enhanced. Conversely, we predicted that exposure to a similar, but not identical, context leads to impaired contextual dependency through memory integration of features of the resembling context. It was also expected that these changes of contextual dependency are contingent on memory reactivation during context (re)exposure (which is important for memory integration to occur, e.g., van Kesteren et al., 2018, 2020; Zeithamova et al., 2012). In a large-scale study, we however did not find support for any of these predictions. We believe that some aspects of the experimental design (e.g., the presentation of many similar looking faces during learning) may have obstructed the formation of unique and easily distinguishable episodic memories and ultimately the occurrence of memory integration.

The procedures adopted in **Chapter 4** were likely more effective in inducing the formation of robust episodic memories and the triggering of memory integration than the previously described method in **Chapter 3**. The aim of this study was to uncover whether contextual (in)stability across similar events determines whether impairment or facilitation of later memory recall occurs. Classic interference theory posits that contextual stability is a source of memory weakening, while contextual variability protects against such interference (Anderson, 2003). However, integration theory predicts the opposite: i.e., enhanced recall in case of contextual stability across overlapping episodes (Chanales et al., 2019; Kuhl et al., 2010; Schlichting & Preston, 2014; Wahlheim, 2015; Zeithamova et al., 2012). We found that when similar events took place in the same spatial context, memory integration occurred and all associations within and across the original memory and the new memory were bolstered. Conversely, for overlapping events that were encoded in different contexts, recall of one memory was accompanied by inaccessibility of the other. These recall patterns were however not permanent, as competition between memories greatly changed in an additional

experiment that included a test in the original encoding context, as opposed to a neutral white background in the first experiments. With contextual reinstatement at test, recall of episodes that were encoded in the same context was relatively impaired, whereas contextually dissimilar memories were protected against interference. These findings thus identify contextual (in)stability across original and related new memories as an important determinant of memory accessibility and show that classic interference theory and integration theory may be reconciled by taking into account contextual conditions during recall.

Chapter 5 addressed a completely different form of memory change, i.e., pharmacological blockade of fear memory reconsolidation. Recent research shows that post-reactivation administration of propranolol (i.e., an amnestic pharmacological agent) can reduce fear responding in humans (Elsey et al., 2018). How potential boundary conditions like memory strength and memory age (e.g., Bustos et al., 2009; Suzuki et al., 2004) can be overcome is however largely unknown, which may hamper successful application in clinical practice. At a more fundamental level, it is unclear through what neurobiological mechanism propranolol disrupts or blocks the reconsolidation of fear memories. To elucidate these issues, we performed a series of experiments in an animal fear-conditioning paradigm, which is ideally suited to not only manipulate key factors like memory strength and age but also assess underlying neurobiological processes. In a series of experiments that included various training protocols, we however did not observe that administration of propranolol after memory reactivation led to reduced fear responding during a later retention test. We also did not find that propranolol affected retrieval-induced neural activity in the hippocampal dentate gyrus. We performed several follow-up experiments to clarify whether these null findings are due to an ineffectiveness of propranolol or whether memory reconsolidation was not triggered. Since post-reactivation administration of anisomycin (i.e., a highly potent amnestic drug, e.g., Nader et al., 2000; Suzuki et al., 2004) also did not reduce fear responding and expression of glutamate receptor subunit GluA2 (a marker of memory destabilization, Bhattacharya et al., 2017; Rao-Ruiz et al., 2011) was not altered by reactivation, it seems that the null findings are best explained by an inability to trigger reconsolidation. Overall, these findings illustrate the current elusive nature of reactivation-dependent changes in non-human fear memory.

2. General considerations

The majority of the studies reported in this dissertation were similar in their overall aim to gain insights into the dynamic nature of memory, and - despite seemingly disparate methods – employed a similar general approach. They involved (i) the induction of a memory, (ii) subsequent manipulation of the formed memory, and (iii) testing whether the memory was altered by this manipulation. Across the individual chapters, it is therefore possible to synthesize key insights regarding each of these phases. In this section, I will in turn address every stage that is needed to study memory change

(formation, manipulation, testing), while highlighting some of the main insights derived from the work presented in this thesis.

2.1. Studying memory change: the importance of robust memory formation. Without successful induction of a memory, a change in memory cannot be studied. To be able to realize this, one does not need to be a seasoned memory researcher. However, several aspects of my PhD trajectory illustrate that inducing robust and well-demarcated memories in the laboratory to subsequently study memory change can be surprisingly difficult. For instance, in **Chapter 1** (Introduction) I briefly described the initial aim of my PhD project. The original plan involved a series of human fear-conditioning studies that included memories of different strengths to test how boundary conditions of memory reconsolidation may be circumvented. Unfortunately however, creating a robust fear memory turned out to be quite challenging and multiple ones of different strengths even more so. Hence, just the practical decisions that were made over the course of my project (e.g., switching to animal models) illustrate that the formation of suitable memories to study memory change is not necessarily easy. My switch to other methodologies notwithstanding, some chapters in this dissertation lead to a somewhat similar conclusion. For example, in **Chapter 3** we found that context reexposure had no effect on the contextual dependency of previously formed neutral and emotional episodic memories. We speculate that this null finding may be due to the stimuli that were used during the first phase of the experiment (i.e., memory formation). The learning trials were highly similar (i.e., they all included a face image), such that participants may have struggled with imagining distinct events and potentially did not form unique episodic memories. If this was indeed the case, then this may explain why subsequent manipulations to change the contextual dependency of specific memories were to no avail. The approaches used in other chapters (in which memory change was successfully studied) provide insights into how the selection of stimulus material could be improved. For example, when preparing the study reported in **Chapter 4,** much effort was put into the creation of word pairs that are suitable to include in the experiments. When selecting words and assembling the word pairs, we made sure that the semantic relationships between all words (i.e., both within word pairs and across all used words) were as low as possible. This may have contributed to the induction of unique episodic memories, which could then be manipulated in a highly specific manner. Hence, using a set of stimuli in which such quality aspects can be both quantified and controlled may in future experiments provide a better basis to study the effects of context reexposure on contextual dependency of memory.

Interestingly, also in the animal fear-conditioning research (**Chapter 5**) some difficulties in the formation of robust memories were encountered. Specifically, in some experiments the freezing levels were so low that one could suspect that the animals had not learned very well and therefore memory change (i.e., reconsolidation) could not be studied. Although this observation is not a convincing explanation of the overall null result (i.e., the freezing levels looked normal in other experiments), it illustrates that

even adopting classic procedures that were successful in the past does not guarantee a suitable protocol. In a previous study that involved the same mouse strain, laboratory space, behavioral system and training and memory reactivation protocols (Rao-Ruiz et al., 2011), overall freezing levels were markedly higher than in the experiments reported here (**Chapter 5**). Apparently, over time unknown changes can occur in laboratory animals or facility conditions that compromise the effectiveness of frequently used protocols to induce robust memory formation.

Thus, across two very different research paradigms, it appears that successfully inducing memories in the laboratory depends on subtle factors. Careful selection of the stimulus material and procedures is therefore needed to make sure that a basic requirement to study memory change is met: the establishment of a robust and demarcated memory.

2.2. Inducing memory change: the importance of new learning. The studies described in this dissertation do not only lead to similar conclusions about the necessary conditions to study memory change, but also about what factors seem key to manipulate memory once it has been successfully formed. For example, the occurrence of new learning may have been a critical factor across several of the chapters. Apart from difficulties in the formation of a robust memory, another potential reason for the null findings in **Chapter 3** is that there was only limited incentive for participants to learn when they underwent context reexposure. When no or little learning takes place, a change in memory does not serve a clear functional purpose and therefore seems unlikely to occur. In the animal research this study was based on (Al Abed et al., 2020; de Oliveira Alvares et al., 2012; Wiltgen & Silva, 2007; Winocur et al., 2009; Zhou & Riccio, 1994), there was an obvious adaptive benefit to learning during context reexposure. For an animal that has received an aversive shock in a particular environment, it is useful to capitalize on a new opportunity to learn the perceptual details of the shock cue, to better predict the occurrence of a threatening event in the future. However, for participants who have seen angry faces and are subsequently reexposed to the context in which these faces were shown, the need to learn is probably much lower (i.e., they have not actually been harmed during the learning phase which may reduce their motivation to learn). Interestingly, in another study included in this dissertation (i.e., **Chapter 4**) participants were forced to learn during the memory manipulation phase (i.e., AC learning to criterion). The fact that this study did show robust memory changes corroborates the idea that new learning could be crucial. Hence, a repetition of the experiment described in **Chapter 3** in which both appropriate care is taken that unique episodic memories are induced (see section 2.1) and new learning is stimulated, may be insightful.

Again, not only the studies in which episodic memories were investigated (e.g., **Chapter 3 and 4**) suggest that new learning is a requirement to induce memory change. Similar arguments apply to the animal fear-conditioning study reported in **Chapter 5**. Indeed, a well-known finding in the reconsolidation literature is that mere retrieval is not enough for a memory to become receptive to change. Destabilization is only triggered

when new information is provided which calls for an update of the memory (Lee, 2009; Pedreira et al., 2004; Sevenster et al., 2012). A lack of learning upon memory reactivation could therefore be one of the reasons we did not observe post-reactivation amnesia in **Chapter 5** (although there is no clear reason why similar protocols effectively triggered reconsolidation in the past, e.g., Rao-Ruiz et al., 2011).

In short, the research reported in this thesis in several ways points to learning upon memory reactivation as an important factor when attempting to induce memory change. Without presentation of new information and sufficient motivation to learn, there is little functional value in changing a memory.

2.3. Interpreting memory change: the importance of testing conditions. Finally, when a robust memory has been formed and subsequent attempts to manipulate this memory have successfully resulted in a change in behavior (e.g., enhanced cued recall performance or reduced freezing), it is important to consider how such data should be interpreted. **Chapter 4** illustrates that one can be easily mistaken when drawing conclusions about the nature of memory change. In this study, we observed – amongst other effects – that new learning can interfere with memory of an overlapping learning event that took place in a different context. In a follow-up experiment (Experiment 2) we also demonstrated that his effect was not explained by source confusion, but reflects an inability to retrieve the original memory. Such findings have in previous research been taken as evidence of a permanent memory change (e.g., through reconsolidation Hupbach et al., 2007, 2009). Crucially however, in the final experiment reported in **Chapter 4** (Experiment 3) we found that reduced original memory retrieval did not at all occur when contextual cues were provided during recall. This shows that memory was likely not "erased" in Experiment 1 and 2. Such "provocations" of memory to gain insights into the nature of memory change are common in fear-conditioning research (e.g., reinstatement tests, Kindt et al., 2009). However, in the episodic memory literature firm tests of the permanence of memory change are rarely included (Elsey et al., 2018). The work presented in this dissertation underscores that this is crucial to perform.

3. Outstanding questions

3.1. Time and new learning events. The passage of time and interference from new learning experiences have been addressed as separate themes in this thesis. It bears mentioning though that these routes towards memory change are far from independent. In fact, time cannot be proposed as an explanation in its own right. Ultimately, the fate of memory is determined by what exactly happens *during* the passage of time and interference is a mechanism to consider in this light. Could some of our insights into the time-dependent transformation of episodic memory, described in **Chapter 2,** be explained by the process of interference, which was the focus of **Chapter 4**? This question is reminiscent of one of the most classic debates in memory research. According to interference theory, forgetting is mainly due to the occurrence of new similar learning events (McGeoch, 1932). Decay theory on the other hand states that

over time memories naturally disintegrate in a way that is independent of new memory formation (Brown, 1958). It is conceivable that interference has indeed played a role in the effects we have observed in **Chapter 2**. Stronger memory loss of neutral than emotional items may have occurred because the emotional items were relatively resistant to interference from new learning experiences outside the laboratory. However, even though interference theory has for a long time dominated the field at the expense of decay theory, the classic debate has recently been reinvigorated with important new insights. For example, preclinical work has shown that a time-dependent memory loss can occur in a way that is independent from the occurrence of new learning experiences by naturally occurring removal of receptors that are critical for memory persistence (Migues et al., 2016). This finding shows that decay theory remains an important candidate to explain changes in memory over time.

Importantly, although interference and decay are competing theories, they are not mutually exclusive. A probable explanation to consider is that both processes play a critical and independent role in the time-dependent changes of episodic memory components we studied in **Chapter 2** (item memory and contextual memory). For instance, it has been proposed that contextual representations may be more sensitive to processes of decay than to interference, as pattern separation in the hippocampus can reduce the impairing influence from new learning experiences. Conversely, memory components that rely on extra-hippocampal structures (e.g., item memory) could be more susceptible to interference processes than to decay (Hardt et al., 2013). Therefore, future research may reveal that both processes contribute to the time-dependent transformation of memory.

When trying to explain time-dependent changes in memory, the potential role of new learning events is thus important to consider. However, the reverse is also true. That is, the effects of similar learning events on previously formed memories may depend on the amount of time that has passed since original learning took place. Time has for instance already been studied and recognized as an important factor in memory integration. It has been suggested that this process only occurs when overlapping events occur on the same day (Zeithamova & Preston, 2017). In line with recent animal research (Pignatelli et al., 2019), we have shown that this boundary condition is not fixed and that new learning can be integrated with consolidated memories when the encoding context is shared (**Chapter 4**). However, as memories tend to further change with additional time (as we have addressed in **Chapter 2**), it is worth to consider how contextual stability across very remote memories may guide memory change. For example, since memories usually become more schematic over time (Barry & Maguire, 2019; Frankland & Bontempi, 2005; Meeter & Murre, 2004; Moscovitch et al., 2016; Tonegawa et al., 2018), it is possible that at some point new learning does not – or to a lesser degree – triggers memory integration since the spatial context is no longer capable to strongly activate the original learning experience. Some studies even suggest that moderate retrieval of a memory can sometimes impair - instead of enhance – memory (Ritvo et al., 2019). If this is true, a memory that after some passage

of time only partially depends on context may interestingly become weakened – not strengthened - by new learning in the same context.

In sum, time and new related learning as we have studied in **Chapter 2** and **Chapter 4**, respectively, are not independent determinants of memory accessibility. These factors can interact in complex ways and it is therefore important to not only study them separately. Future research in which both these factors are systematically varied can provide important contributions to an improved understanding of the dynamic nature of memory.

3.2. Classic interference and emotional memory. One of the main aims in this dissertation was to further the understanding of how emotional memories can be therapeutically altered (**Chapter 3 and Chapter 5**). Also, a substantial part of the thesis was concerned with changes in non-emotional memory (**Chapter 4**). A remaining question to consider is whether the knowledge we have gained about the changeability of neutral memory can be translated to emotional memory. Traditionally, these fields have developed in relative isolation, even though parallels exist between the two. For instance, extinction training in which the learning of new information (CS-noUS) results in diminished expression of the fear memory (CS-US) is a form of interference that in several ways resembles the interactions between neutral word pairs (AB/AC) (Polack et al., 2017). It is well-known that the expression of fear memories (CS-US) is progressively extinguished during the learning of new safe information (CS-noUS) (Vervliet et al., 2013). This effect of new safety learning is stimulus-specific, as fear responding to a different CS that was also paired with the US during double-cue fear learning does not become suppressed (i.e., CS_1-noUS learning interferes with CS_1-US, but not with CS_2-US, e.g., Sau et al., 2012). Research into non-emotional memory has shown that AC learning reduces original memory accessibility in a similar, gradual way (Barnes & Underwood, 1959) and also specifically for the AB association but no other pairings with the B associate (Wang et al., 2015). Furthermore, it has often been demonstrated that fear returns after substantial time has passed since extinction training (spontaneous recovery, e.g., Hermans et al., 2006). Likewise, researchers using paired associates learning have shown that - with time - AB memory may recover from interference by AC learning (Silverstein, 1967). Based on such findings, it is argued that AC learning does not lead to unlearning of the AB memory, but that the two associations compete for recall during retrieval (i.e., response competition theory, Anderson, 2003). This matches current consensus among affective neuroscientists, stating that CS-US and CS-noUS associations are competitors in controlling responding to the CS (Bouton, 2002).

In **Chapter 4**, it has become clear that contextual similarity across AB and AC learning leads to integration and bolstered memory. Given the similarities between how AB/AC and CS-US/CS-noUS memories can interact as described above, should one expect the same contextual influence over the effects of extinction training on fear memories? The existing empirical evidence at first sight seems to indicate that this is not the case. For example, it has been shown that AAC fear-conditioning designs (referring to conditioning and extinction in the same context but memory testing in a different

context) leads to larger fear renewal than ABC designs (i.e., contextual dissimilarity across conditioning, extinction, and testing) (Laborda et al., 2011). In other words, contextual similarity here does not lead to enhancement of the original memory but rather stronger impairment, such that the effects in both paradigms seem incomparable. However, when one more closely considers the meaning of the provided information in each paradigm, the respective findings may in fact point to the same process. In AB/AC learning (e.g., "Cigar-Book", "Cigar-Net"), the B and C elements ("Book" and "Net") are not in conceptual conflict per se and theoretically can co-exist in a meaningful and non-opposing way (i.e., "Book" and "Net" do not intrinsically carry contradictory meanings). The same cannot be said about CS-US and CS-noUS associations, as these associations have opposite content (i.e., the CS is dangerous and the CS is safe, respectively, see Hupbach, 2011 for a similar argument). Therefore, it is possible that in both cases the same process is triggered (integration) but the consequences of this process are inverted (i.e., cooperation between B and C versus competition between US and noUS). In line with this idea, recent research suggests that effective extinction training, rather than simply leading to the formation of an independent safety memory, depends on reactivation of the fear memory during safety learning such that an integration of the fear memory and extinction training takes place (Khalaf et al., 2018).

Thus, the insights that are gained by studies in which AB/AC paired associates learning is employed may be more informative for emotional memory change than may initially seems to be the case. At the same time, it is of course clear that changes in declarative memory do not necessarily go hand in hand with conditioned psychophysiological responses (Squire, 2004). In future research, it may therefore be fruitful to adopt paradigms in which both memory aspects are incorporated (de Vries et al., 2021). For example, one could test whether integration of safety information into a fear memory leads to bolstered declarative memory (i.e., like what we have observed in **Chapter 4**) but decreased psychophysiological responding to the CS (as the meaning of the fear memory and the safety memory are in direct conflict such that competition occurs). Hence, provided that the similarities and differences between non-emotional and emotional memory research paradigms are thoroughly compared, our novel insights into neutral memory change by new learning may be translated to fear memories.

4. Applications and translational considerations

4.1. Education and eyewitness testimony. The knowledge we have gained about when episodic memories become strengthened or weakened (**Chapter 4**) bears clear practical implications. It is important to consider the exact circumstances under which one can expect these memory changes to occur though, as they can be easily misunderstood. In educational settings, one could for instance suspect that consistently teaching in the same classroom should be beneficial to remember learned material in a different context (e.g., the exam room). Indeed, we have shown that a stable spatial context can elicit memory integration and subsequently improved recall in a new context. It is important to note however that in our study we specifically aimed to

model episodic memories, which include what-where-when qualities and a recollective experience during recall (Tulving, 2002). Students who read in a book or listen to a talk may not necessarily form episodic memories that involve firm associations between the course material and the spatial environment. Since powerful context-induced memory retrieval during new learning then may not take pace, boosted recall occurs to only a small extent or not at all. Apart from the episodic nature of memory, familiarity with the spatial context is a factor to consider for similar reasons. When students become more familiar with their study environment over time, the extent to which the spatial context triggers memory retrieval of earlier learning events could decrease such that the memory benefits become smaller. Related to this idea, it has been shown that contextual reactivation of episodic memory does not result in a reconsolidation-dependent memory update when participants are highly familiar with the context (Hupbach et al., 2011). It even seems that learning in different classrooms can be beneficial, as the contexts can be used to chunk individual classes, thereby providing a better overview of the learning material (Smith et al., 1984). For these reasons, application of our findings is preferably viewed in relation to memory of specific events and the strategies that call upon such type of memories. For example, the method-of-loci involves the imagination of an event in which one encounters to-be-remembered items along a specific route (Wagner et al., 2021), which is reminiscent of the episodic memory enhancement by contextual stability we have observed. An important practical insight from our study is that the accessibility of similar episodic memories depends on whether contextual information is presented during recall. Upon a return to the context in which original learning took place, contextual variability rather than similarity seems to be beneficial for memory recall.

Apart from education, the findings in **Chapter 4** are also – or perhaps even to a greater degree - relevant for forensic settings. The witnessing of a crime conceivably leads to the creation of a true episodic memory (e.g., what happened during the crime, when it happened, and when) and so does the subsequent experience of being interviewed by law enforcement (i.e., testimony). Interference with memory of a crime and confusion about which pieces of information belong to which event (i.e., crime versus later events) is a notorious problem in the legal system (Loftus, 2005). For example, "bait questions" during interviews could contribute to disruptive misinformation effects on later memory recall (Luke et al., 2017). The insights we have gained into how spatial context both directs accurate recall of memory as well as source memory could be helpful in this light. We have shown that a new overlapping episodic memory that occurs in the same spatial context as the original learning event bolsters recall of both events. Furthermore and crucially, we have also demonstrated that memory of which event occurred on which day (i.e., source memory) is enhanced and memory misattributions are relatively reduced. Perhaps one can thus hypothesize that interviewing eyewitnesses at the crime scene (when practically possible) could not only bolster memory of the crime itself and what was covered during questioning, but also reduce confusion between the two. Apart from its purpose in

the collection of initial evidence, testimony interviews might thereby be transformed from an unavoidable source of interference to an enhancer of crime-related memory.

Before any procedural recommendations are in place, translational research is of course essential to bring laboratory studies closer to real-life memories. Interestingly, there are already some reports of experimentally-induced changes in episodic memories that are acquired outside the laboratory (St. Jacques et al., 2013; St Jacques & Schacter, 2013). In these studies, participants were sent on a museum tour during which photographs were automatically made from all individual stops they made along the way (e.g., at a display case). The photographs were then used to study memory of the tour in the laboratory. The authors presented the participants with these images and sometimes showed a photograph from a different museum tour they never went on immediately afterwards (i.e., as a lure). During a later memory test, they found that recollection during presentation of a photograph from the original tour predicted accurate memory for that event, but also false memory of the lure (i.e., they were mistakenly identified as a stop they had made along the way). This study has two important implications. First, somewhat contrary to our observations in **Chapter 4,** retrieval of a memory can apparently sometimes lead to increased memory misattributions. Therefore, the exact circumstances under which source memory becomes enhanced or impaired needs further study before conclusions can be drawn for applications of such findings in practice. Second, this paradigm could be capitalized on to translate the findings in **Chapter 4** to real-life memories. For example, one could let participants either take one museum tour or two similar tours in the same museum to test if bolstered memory occurs by contextual similarity (i.e., the museum) across similar events.

4.2. Context processing and PTSD. In this dissertation, contextual dependency of emotional memory was one of the main themes. We have investigated its natural development over time (**Chapter 2**) and whether context reexposure may alter it (**Chapter 3**). These studies have been carried out partly based on the idea that reduced contextual dependency of emotional memory is a significant vulnerability factor in the development of anxiety disorders and PTSD. It is important to consider the evidence for this argument and whether the laboratory findings will thus indeed likely translate to real-life disorders. PTSD is of course a condition that involves many characteristics and etiological factors (not only reduced contextual dependency but also e.g., feelings of guilt, incorrect interpretation of other people's reactions to one's trauma, and many more Ehlers & Clark, 2000). The studies we have conducted here were not intended to model the full scope of what constitutes such a complex phenomenon. Nevertheless, laboratory findings could contribute to a better understanding of the memory distortions observed in PTSD. For example, it has been shown that low contextual dependency of memory predicts the occurrence or the distress of intrusions that are elicited by watching a distressing film (Bisby et al., 2010; Meyer et al., 2017; Voorendonk et al., 2021). Moreover, it is clear that people who have been diagnosed with PTSD show reduced associative memory (including contextual memory) relative to control

participants who have not experienced trauma or trauma-exposed individuals who have not developed PTSD (Lambert & McLaughlin, 2019). Therefore, it seems that insights based on laboratory experiments like we have conducted here relate to clinical presentations. Whether low contextual dependency is a vulnerability factor rather than a consequence of the development of PTSD is not yet known. Collecting longitudinal data will thus be important to demonstrate if PTSD can be prevented by targeting contextual dependency of emotional memory.

Assuming that processing of context indeed plays an important role in the emergence of PTSD, the hypothesis we tested in **Chapter 3** and the findings in **Chapter 4** could indicate that revisiting the context in which an emotional event occurred has therapeutic effects. It may for example restrict generalization of fear memories to new contexts (i.e., which was the premise of **Chapter 3**). Furthermore, as contextual similarity across events leads to memory integration and enhanced recall (**Chapter 4**), one can hypothesize that a return to a trauma context may enable therapists to improve the coherence and narrative structure of patients' trauma memories (i.e., which may be compromised in PTSD, Brewin, 2011, but see Rubin et al., 2016). For such purposes, a return to the context likely does not need to be performed in vivo but can take place in the patient's imagination. Imagery rescripting has been shown to be effective for several disorders, including PTSD (Boterhoven de Haan et al., 2017, 2020; Morina et al., 2017; Reiss et al., 2017). Although this intervention mostly focuses on emotional hotspots, some elements of the treatment protocol may work by directing the patient's attention to context. For example, during the imagery part of the treatment, therapists routinely ask their patients: "what do you see, what do you hear, what do you feel, what do you smell?" (Arntz & van Emmerik, 2020). This may aid in retrieving contextual information, such that subsequently rescripted scenes of the trauma are integrated with the trauma memory. If this is true, additional emphasis on retrieving the exact trauma context may even further improve the effects of this treatment. Indeed, the study into the mechanisms underlying the effects of imagery rescripting is just starting (Bosch & Arntz, 2021; Kunze et al., 2019). A mediating role for contextual processing has already been mentioned (Bosch & Arntz, 2021) but – to my knowledge - not yet demonstrated. Given its role in episodic memory change as shown in **Chapter 4** (and hypothesized in **Chapter 3**), retrieving the trauma context may be considered as a potentially conducive element of imagery rescripting.

4.3. Reconsolidation-based interventions. Translational attempts have already had some success in memory reconsolidation research. For example, a convincing demonstration of post-reactivation amnesia in people with fear of spiders suggests that fundamental insights into memory plasticity can be applied in clinical settings (Soeter & Kindt, 2015a). However, as some other treatment studies did not show the same promising results (Elsey et al., 2020; Elsey & Kindt, 2021; Roullet et al., 2021; Wood et al., 2015), it is clear that a reconsolidation-based intervention does not always work flawlessly. Together with null findings in preclinical research (**Chapter 5** and e.g., Schroyens et al., 2019),

these data indicate that it is far from perfectly understood how the process of memory reconsolidation can be successfully triggered. It is therefore important to consider what approach may help to improve control over the ubiquitous though subtle amnestic effects that have been observed in previous research (Elsey et al., 2018; Jardine et al., 2022).

To advance our understanding of memory reconsolidation, it seems crucial to first discern what may explain the recent null findings. The results presented in **Chapter 5** and in other papers (Rotondo et al., 2022) show that they are most likely a result of difficulties in consistently inducing memory destabilization. We have observed that expression of glutamate receptor subunit GluA2 (i.e., a marker memory destabilization) was not significantly altered by memory reactivation (**Chapter 5**). Similarly, Rotondo et al. (2022) found no reduction in Shank protein expression (i.e., another marker of destabilization, Lee et al., 2008). These findings thus seem to indicate that protocols which previously led to memory destabilization (Dębiec & Ledoux, 2004; Rao-Ruiz et al., 2011) are no longer or much less effective in doing so. Since the occurrence of reconsolidation has been shown to be gated by several factors (e.g., memory strength and age are well-known boundary conditions, Suzuki et al., 2004; Bustos et al., 2009), it seems straightforward to reason that there are other - currently unknown - influences at play that prevent the occurrence of post-reactivation amnesia. Pointing to unspecified boundary conditions is not an ideal approach when trying to explain null findings though, as it limits the possibilities to falsify any phenomenon (Elsey & Kindt, 2017). Therefore, it is relevant to provide explanations that can be tested empirically.

An explanation that could be considered is early life stress (which is known to influence memory plasticity, Villain et al., 2018; Couto-Pereira et al., 2019) and other rearing conditions. When using animals ordered from a commercial breeder, researchers do not have sight or control over these factors. For this reason, using animals that are bred in-house may be helpful, although this will not guarantee high replicability. Recently, it has been shown that differences in rearing conditions between laboratories can have a pronounced impact on animals' phenotypes, including emotional responding and synaptic plasticity in the hippocampus (which are highly relevant factors when studying contextual fear memories like in **Chapter 5**) (Jaric et al., 2022). Hence, a multicenter trial in which animals undergo classic procedures to induce reconsolidation in one of several randomly selected laboratories may be insightful. Through such an approach, one could determine whether rearing conditions are indeed partly responsible for the recent null findings and perhaps identify the circumstances under which the effects of amnestic agents on reactivated memories are most robust. What may also be useful is to systematically vary classic factors that are already known to be an important determinant in the induction of memory destabilization (e.g., the duration of memory reactivation, Merlo et al., 2014; Sevenster et al., 2014). The findings described in **Chapter 5** contribute to this strategy, as do other large-scale studies (Rotondo et al., 2022; Schroyens et al., 2019). So far, this has not resulted in improved control over reactivation-dependent amnesia, but additional and well-powered attempts are still relevant to perform. Since overall freezing levels were much lower in the study presented

in **Chapter 5,** compared to a previous study from the same laboratory (Rao-Ruiz et al., 2011), another possibility is that animals have changed their defensive strategy (e.g., from passive freezing to active fleeing). Hence, employing different paradigms such that the effects of post-reactivation administration of amnestic agents can be tested on more than one defensive strategy could also be an option.

It is worth mentioning that if any approach leads to regained control over post-reactivation amnesia, this will not guarantee subsequent translational success. For example, if a multi-center trial shows that post-reactivation amnesia only occurs in a specific rearing condition when a specific procedure is used that involves a specific behavioral measure, it may be difficult to consistently induce such effects in clinical practice. Indeed, those effects that depend on a multitude of subtle conditions in preclinical settings are believed to be the ones that are most difficult to translate (i.e., the standardization fallacy, Voelkl et al., 2021). Considering that post-reactivation amnesia has previously been demonstrated in many paradigms (Jardine et al., 2022) and several successes in experimental human studies have been reported (Elsey et al., 2018), translation seems within the realm of possibility though. Therefore, fundamental research seems critical to identify determinants of the occurrence of memory reconsolidation. The success of a reconsolidation-based intervention will be determined by which variables can be identified as crucial and the extent to which such factors are controllable in clinical settings.

5. Conclusion

Some memories are transient, while others can persist for a lifetime. When an event is stored in memory, its initial representation partly determines whether transience or persistence will likely follow. For example, emotional memories are processed in such a way that they have a smaller chance to decay than neutral memories. However, with the passage of time, new events can occur that drastically change the original course of memory. Neutral memories that were fading can become strengthened. Conversely, emotional events that seemed destined to forever occupy a central place in memory may become relatively silent. The present thesis has contributed to a better understanding of this dynamic nature of memory. For example, it has become clear that the natural development of human episodic memory over time is markedly different for emotional and neutral events. Also, we now have a better understanding of the circumstances under which memories of similar events strengthen each other or compete. The research presented in this thesis additionally illustrates that gaining insights into memory change is far from easy. Subtle conditions need to be met in order to study, induce, and interpret changes in readouts of memory. Provided that these requirements are effectively dealt with, future research may extend and integrate the insights conveyed by this thesis. Thereby, valuable applications may become within reach, ranging from improved memory techniques to bolster information retention in education, to measures aimed at counteracting false memory in forensic settings, to the development of interventions that effectively target disorders of emotional memory.

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SUMMARY

1. Background

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

Forgetting is often associated with daily frustrations, such as not being able to recall where one has parked the car. The case description described above illustrates however that forgetting is important, and that 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. Rather than retaining as many events as possible in as much detail as possible, having the crucial pieces of information available that one particularly needs at the right moment is what helps us thrive. For this reason, 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 aimed to unravel parts of the dynamic nature of memory and focused on several classic factors in particular.

2. Overall approach and purpose

The majority of the studies described in this thesis followed the same classic approach to study memory change in the laboratory. They involved (i) the formation of a memory,

(ii) subsequent manipulation of the formed memory, and (iii) testing whether the memory was altered by this manipulation. However, the exact procedures adopted during these phases varied markedly between the chapters. In order to study episodic memory, we let participants complete a computer task during which we presented them with pictures of spatial environments (e.g., a living room) on which one or several words appeared (e.g., "Cigar" and "Book"). The participants were instructed to come up with a vivid scene that involves a visual representation of the words in the environment of the context image. In this way, we aimed to model episodic memories that contain what-where-when qualities that result in a recollective experience when the memory is retrieved. During the next experimental session, we performed manipulations that were aimed at inducing either forgetting or strengthening of the previously formed memories. In the final experimental session, we tested the success of these manipulations by assessing memory of the originally formed events (e.g., cued recall tests). Insights obtained through such experiments could be relevant for educational (effective learning techniques) or forensic settings (accuracy of eyewitness testimonies).

We were however not solely interested in changes in neutral episodic memories. Since emotional memories lie at the root of affective disorders, it is also important to uncover how these memories can be changed (e.g., how emotional responses that occur when retrieving such memories can be diminished). To study emotional memory and compare it with neutral memory, we sometimes e.g., added emotional words (e.g., "Murder") to the imagination task that the participants performed. We also made use of a classic fear-conditioning procedure. In this research paradigm, experimental animals or humans receive an electrical shock that is signaled by a stimulus (e.g., a visual, auditory, or spatial cue). After sufficient pairing of these two stimuli, a fear memory is formed, involving an association between the conditioned stimulus (CS, cue) and the unconditioned stimulus (US, shock). Evidence for a fear memory trace is typically shown when the CS alone (i.e., without the shock) triggers a conditioned fear response (CR, freezing). In a subsequent experimental session, manipulations to alter fear responding can be implemented. In the final session, the success of these manipulations (e.g., reduced freezing) are tested using a fear memory retention test (e.g., by exposing subjects to the CS and measuring whether their fear responding to this stimulus has now changed).

3. Main insights

The main conclusions that can be drawn from the research presented in this thesis are as follows. First, it has become clear that studying memory change can be very difficult. We observed that the success of each of the involved experimental phases (i.e., memory formation, memory manipulation, and memory testing) depends on subtle conditions. For the formation of memories that can be studied in the laboratory, it is imperative that stimulus materials that are used to induce learning events are both sufficiently distinctive and incite engagement. This is a requirement for the establishment of well-demarcated and robust memories to potentially change during the next phase (i.e.,

manipulation). We also reason that for successful memory manipulation, new learning is essential. Without presentation of new information and sufficient motivation to learn, there is little functional value in changing a memory. Finally, when a robust memory has been formed and subsequent manipulations have resulted in a change in behavior (e.g., enhanced cued recall performance or reduced freezing), this does not necessarily mean that this memory has been permanently modified. For example, when a memory manipulation has caused markedly impaired recall, this cannot be taken as evidence that memories have been forgotten for good. We have shown that with altered recall conditions (e.g., performing testing in the same spatial context as during learning), a memory that seemed otherwise impossible to recall could be retrieved with ease.

Apart from general takeaways about how to properly investigate memory change, our studies also provide new theoretical insights into the dynamic nature of memory. It is already well-known that the central elements of events (often termed "items") are relatively strengthened in memory when they are emotional (e.g., the perpetrator in a witnessed crime). This privileged remembering of emotional events does not occur for all memory elements though: memory for peripheral details (e.g., the spatial environment in which an event took place) is often impaired for emotional versus neutral events. Retrieval of memory is usually 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. Due to its strong item, but weak context representations, such contextual dependency of memory is reduced for emotional events. We have extended previous research by showing how these subcomponents of episodic memory (i.e., item memory and contextual dependency) develop over time. Specifically, we have observed that, with time, item memory becomes increasingly stronger, but contextual dependency increasingly weaker for emotional events.

Next to effects of time, we delved into the influence that new events can have on previously formed memory (i.e., retroactive effects) and existing memory can have on recall of new events (i.e., proactive effects). Memories for events that are similar (i.e., show overlap in content) sometimes strengthen each other, but at other times compete, causing facilitation or impairment of retrieval, respectively. For a long time, it has remained elusive when exactly one (i.e., interference) or the other (i.e., facilitation) process occurs. In a study reported in this dissertation, we have partly solved this paradox. Specifically, we have shown that when similar events take place in the same spatial context, all associations within and across these events are strengthened. Conversely, for similar events occurring in different contexts, interference occurs such that recall of one memory is accompanied by inaccessibility of the other. These recall patterns were however not permanent. When recall was tested in the context in which learning had taken place, contextual stability across events resulted in impaired recall, whereas contextual variability protected against interference. This study thus shows that spatial context across similar events and later retrieval attempts modulates whether episodic memory becomes enhanced or impaired.

4. Conclusion

Some memories are transient, while others can persist for a lifetime. When an event is stored in memory, its initial representation partly determines whether transience or persistence will likely follow. For example, emotional memories are processed in such a way that they have a smaller chance to decay than neutral memories. However, with the passage of time, new events can occur that drastically change the original course of memory. The present thesis has contributed to a better understanding of this dynamic nature of memory. It has become clear that subtle conditions need to be met in order to study, induce, and interpret changes in memory. Provided that these requirements are effectively dealt with, future research may however extend the insights conveyed by this thesis. Thereby, valuable applications may become within reach, ranging from improved memory techniques to bolster information retention in education, to measures aimed at counteracting false memory in forensic settings, to the development of interventions that effectively target disorders of emotional memory.

NEDERLANDSE SAMENVATTING

1. Achtergrond

In het jaar 2000 zocht een vrouw hulp bij James L. McGaugh (een pionier in de wetenschap van leren en geheugen) voor een hoogst ongewoon geheugenprobleem. Zij beschreef dat haar geheugen voor persoonlijk ervaren gebeurtenissen zo uitgebreid en krachtig was dat zij vaak overweldigd werd door haar eigen herinneringen aan het verleden. Het ophalen van één gedetailleerde herinnering leidde tot het activeren van een volgende en een volgende, hetgeen resulteerde in een eindeloze, oncontroleerbare en uitputtende golf van associaties. Dr. McGaugh en zijn collega's waren zowel nieuwsgierig als sceptisch over dit verhaal en spraken af met deze vrouw. Vervolgens voerden zij gedurende een aantal jaren tests uit om inzicht te krijgen in haar geheugencapaciteiten. Hoewel de meeste van deze capaciteiten gemiddeld waren en sommige zelfs onder gemiddeld, bleek dat zij zich persoonlijk ervaren gebeurtenissen buitengewoon goed kon herinneren, met name die met betrekking tot datums. Wanneer men bijvoorbeeld een willekeurige datum van jaren geleden noemde, kon zij de betreffende dag van de week (b.v. woensdag) en vele details van wat er die dag was gebeurd met gemak terughalen. Ze was uiterst consequent en bijna volledig accuraat, zoals bleek uit een dagboek dat ze had bijgehouden van haar 10e tot haar 34e levensjaar en nieuwsfeiten die over verschillende decennia hadden plaatsgevonden. Neuropsychologische tests toonden ook aan dat ze een uitzonderlijk vermogen had om - wat men noemt - episodisch geheugen te vormen (d.w.z. herinneringen waarbij men terughaalt wat er tijdens een gebeurtenis gebeurde, waar het gebeurde en wanneer). De auteurs vermoedden dat haar vermogens te herleiden waren naar een nogal obsessieve neiging om op een zeer gestructureerde manier te onthouden wat er op elke dag was gebeurd. Het leek erop dat deze vrouw hier uiteindelijk zo goed in was geworden dat ze nu geconfronteerd werd met gevolgen die zelfs een ervaren geheugenonderzoeker niet had kunnen voorzien: zich regelmatig opdringende, irrelevante herinneringen aan vroegere gebeurtenissen.

Vergeten wordt vaak geassocieerd met frustraties in het dagelijks leven, zoals het niet kunnen herinneren waar men de auto heeft geparkeerd. De hierboven beschreven casus illustreert echter dat vergeten belangrijk is en dat het meest effectieve geheugensysteem niet vergelijkbaar is met een opslagruimte die zoveel mogelijk informatie bevat. Het is de flexibiliteit van het geheugen die de sleutel vormt tot een optimale aanpassing aan de omgeving. Wij gedijen het beste als wij cruciale informatie tot onze beschikking hebben wanneer wij deze nodig hebben, in plaats van als zoveel mogelijk gebeurtenissen in zoveel mogelijk detail worden vastgehouden. Om deze reden is het niet verwonderlijk dat onderzoek naar veranderingen van het geheugen zeer actueel is in de psychologische wetenschap en de neurowetenschappen. Vele decennia van onderzoek hebben al uitermate belangrijke inzichten opgeleverd in hoe herinneringen transformeren: van verloren gaan, tot versterkt worden, tot vervormd raken. Tegelijkertijd is een gedetailleerd begrip van hoe herinneringen veranderen nog lang niet bereikt, omdat een veelheid aan belangrijke vragen vooralsnog onopgelost

is. In dit proefschrift is getracht delen van de dynamische aard van het geheugen te ontrafelen. Hierbij zijn hoofdzakelijk enkele klassieke factoren belicht.

2. Algemene benadering en doel

De meeste van de in dit proefschrift beschreven studies volgden dezelfde klassieke aanpak om geheugenverandering in het laboratorium te bestuderen. Ze omvatten (i) de vorming van een herinnering, (ii) een daaropvolgende manipulatie van de gevormde herinnering en (iii) het testen of de herinnering door deze manipulatie is veranderd. De precieze procedures die in deze fasen werden gevolgd, verschilden echter sterk van hoofdstuk tot hoofdstuk. Om episodisch geheugen te bestuderen, lieten wij deelnemers een computertaak uitvoeren waarbij wij hen afbeeldingen presenteerden van ruimtelijke omgevingen (b.v. een huiskamer) en waarop één of meerdere woorden werden getoond (b.v. "sigaar" en "boek"). De deelnemers werden geïnstrueerd om een levendige gebeurtenis te bedenken waarbij een visuele voorstelling van de woorden in de contextafbeelding wordt gevormd. Op deze manier trachtten wij episodische herinneringen te modelleren die wat-waar-wanneer kwaliteiten bevatten. Tijdens de volgende experimentele sessie voerden wij manipulaties uit die ofwel gericht waren op het verzwakken, dan wel het versterken, van de eerder gevormde herinneringen. In de laatste experimentele sessie testten wij de geslaagdheid van deze manipulaties door de herinneringen aan de oorspronkelijk gevormde gebeurtenissen te toetsen (bv. middels het aanbieden van geheugencues en bij te houden hoeveel herinneringen konden worden opgehaald). De inzichten die worden verkregen met dergelijke experimenten kunnen relevant zijn voor het onderwijs (denk aan effectieve leertechnieken) of in forensische settingen (denk aan de betrouwbaarheid van ooggetuigenverklaringen).

Wij waren echter niet louter geïnteresseerd in veranderingen in neutrale episodische herinneringen. Aangezien emotionele herinneringen aan de basis liggen van affectieve stoornissen, is het tevens belangrijk om te bepalen hoe deze herinneringen kunnen worden veranderd (bv. hoe emotionele responsen die optreden bij het ophalen van zulke herinneringen kunnen worden verminderd). Om emotioneel geheugen te kunnen bestuderen en te vergelijken met neutraal geheugen, voegden we soms emotionele woorden (b.v. "moord") toe aan de inbeeldingstaak die de deelnemers uitvoerden. We maakten ook gebruik van een klassieke angstconditioneringsprocedure. In dit onderzoeksparadigma krijgen proefdieren of mensen een elektrische schok na presentatie van een stimulus (bv. een visuele, auditieve of ruimtelijke cue). Nadat deze twee stimuli frequent genoeg gezamenlijk zijn opgetreden ontstaat er een angstgeheugen, waarbij een associatie is gevormd tussen de geconditioneerde stimulus (CS, cue) en de ongeconditioneerde stimulus (US, schok). Het bestaan van een angstgeheugen wordt gewoonlijk als bewezen beschouwd als presentatie van alleen de CS (d.w.z. zonder de schok) een geconditioneerde angstrespons (CR, bevriezing) teweegbrengt. In een volgende experimentele sessie kunnen manipulaties worden uitgevoerd om de angstreactie te veranderen. In de laatste sessie wordt de geslaagdheid van deze manipulaties (bv. verminderde bevriezing) getest met behulp

van een angstgeheugentest (bv. door proefpersonen bloot te stellen aan de CS en te meten of hun angstreactie op deze stimulus nu veranderd is).

3. Belangrijkste inzichten

De belangrijkste conclusies die kunnen worden getrokken uit het onderzoek in deze dissertatie zijn de volgende. Ten eerste is het duidelijk geworden dat het bestuderen van geheugenverandering zeer moeilijk kan zijn. We hebben waargenomen dat het slagen van elk van de betrokken experimentele fasen (d.w.z. geheugenvorming, geheugenmanipulatie en geheugentests) afhangt van subtiele condities. Voor de vorming van herinneringen die in het laboratorium bestudeerd kunnen worden, is het noodzakelijk dat de stimulusmaterialen die gebruikt worden om leergebeurtenissen te induceren zowel voldoende onderscheidend zijn als aanzetten tot actieve deelname. Dit is een vereiste voor de vorming van goed afgebakende en robuuste herinneringen om vervolgens te kunnen veranderen tijdens de volgende fase (manipulatie). We concluderen ook dat voor succesvolle geheugenmanipulatie nieuw leren essentieel is. Als er geen nieuwe informatie wordt gepresenteerd of er onvoldoende motivatie is om hierover leren, heeft het veranderen van een herinnering weinig functionele waarde. Tenslotte, wanneer er een robuust geheugen is gevormd en latere manipulaties hebben geresulteerd in een verandering in gedrag (b.v. verbeterde prestatie tijdens een herinneringstaak of verminderd bevriezingsgedrag) hoeft dit nog niet te betekenen dat de herinnering blijvend is veranderd. Bijvoorbeeld, als een geheugenmanipulatie heeft geleid tot een duidelijk verminderd vermogen om een herinnering op te halen, kan dit niet worden opgevat als bewijs dat herinneringen voorgoed zijn vergaan. Wij hebben namelijk aangetoond dat met veranderde testcondities (bv. wanneer testen plaatsvindt in dezelfde ruimtelijke context als tijdens het leren), een gebeurtenis die anders onmogelijk leek om te worden herinnerd met gemak kon worden teruggehaald.

Naast algemene inzichten over hoe geheugenverandering goed kan worden onderzocht, leveren onze studies ook nieuwe theoretische inzichten op over de dynamische aard van het geheugen. Het was al bekend dat de centrale elementen van gebeurtenissen (vaak “items” genoemd) relatief versterkt worden in het geheugen wanneer ze emotioneel zijn (bv. herinneringen aan de dader van een misdrijf). Dit preferentiële herinneren van emotionele gebeurtenissen gebeurt echter niet voor alle geheugenelementen: het geheugen voor perifere details (bv. de ruimtelijke omgeving waarin een gebeurtenis plaatsvond) is vaak verzwakt voor emotionele gebeurtenissen ten opzichte van neutrale gebeurtenissen. Het ophalen van herinneringen is meestal sterker wanneer men terugkeert naar de ruimtelijke context waarin een gebeurtenis plaatsvond, in vergelijking met een context die geen verband houdt met de leergebeurtenis. Door de sterke item- maar zwakke contextrepresentaties is deze contextuele afhankelijkheid van het geheugen echter verminderd voor emotionele gebeurtenissen. Wij hebben kennis op basis van eerder onderzoek uitgebouwd door te laten zien hoe deze subcomponenten van episodisch geheugen (d.w.z. itemgeheugen en contextuele afhankelijkheid) zich over de loop van de tijd ontwikkelen. Wij hebben

specifiek waargenomen dat, met de tijd, het itemgeheugen steeds sterker maar de contextuele afhankelijkheid juist zwakker wordt voor emotionele gebeurtenissen.

Naast de effecten van tijd, hebben we ons verdiept in hoe nieuwe gebeurtenissen eerder gevormd geheugen kunnen beïnvloeden (d.w.z., retroactieve geheugeneffecten) en hoe bestaand geheugen invloed heeft op het herinneren van nieuwe gebeurtenissen (d.w.z., proactieve geheugeneffecten). Geheugen voor gebeurtenissen die op elkaar lijken (die inhoudelijke overlap vertonen) kunnen elkaar soms versterken maar op andere momenten juist interfereren met elkaar, waardoor ze respectievelijk het ophalen van de herinneringen vergemakkelijken of belemmeren. Vooralsnog is het onduidelijk wanneer precies het ene proces (d.w.z. interferentie) of het andere proces (d.w.z. versterking) plaatsvindt. In een studie gerapporteerd in dit proefschrift hebben we deze kwestie gedeeltelijk opgehelderd. We hebben aangetoond dat wanneer gelijkende gebeurtenissen plaatsvinden in dezelfde ruimtelijke context alle associaties binnen en tussen deze gebeurtenissen versterkt worden. Omgekeerd, bij gelijkende gebeurtenissen die in verschillende contexten plaatsvinden treedt interferentie op, zodat het oproepen van de ene herinnering gepaard gaat met het ontoegankelijk worden van de andere. Deze geheugenpatronen waren echter niet permanent. Wanneer de herinneringen werden getest in de context waarin het leren had plaatsgevonden, resulteerde contextuele stabiliteit tussen gebeurtenissen juist in verslechterd ophalen van de herinnering, terwijl contextuele variabiliteit bescherming bood tegen interferentie. Deze studie toont dus aan dat de ruimtelijke context waarin gelijkende gebeurtenissen plaatsvinden en latere pogingen om de herinneringen op te halen worden uitgevoerd bepalend is voor het verzwakt of versterkt raken van episodisch geheugen.

4. Conclusie

Sommige herinneringen zijn vergankelijk, terwijl andere een leven lang kunnen standhouden. Wanneer een gebeurtenis in het geheugen wordt opgeslagen, bepaalt de oorspronkelijke representatie van de herinnering gedeeltelijk of deze zal vergaan of voortbestaan. Emotionele herinneringen worden bijvoorbeeld zo verwerkt dat ze een kleinere kans hebben om te vergaan dan neutrale herinneringen. Met het verstrijken van de tijd kunnen echter nieuwe gebeurtenissen zich voordoen die het oorspronkelijke verloop van het geheugen drastisch doen veranderen. Deze dissertatie heeft bijgedragen aan een beter begrip van dit dynamische karakter van het geheugen. Het is duidelijk geworden dat aan subtiele condities moet worden voldaan om veranderingen in het geheugen te bestuderen, te induceren en te interpreteren. Op voorwaarde dat er op succesvolle wijze met deze voorwaarden wordt omgegaan, kan toekomstig onderzoek voortborduren op de inzichten die dit proefschrift heeft opgeleverd. Daarbij kunnen mogelijk waardevolle toepassingen bereikt worden, variërend van verbeterde technieken voor het vasthouden van informatie in het onderwijs, tot manieren om valse herinneringen in forensische settingen tegen te gaan, tot effectieve behandelingen van stoornissen waaraan emotioneel geheugen ten grondslag ligt.

PUBLICATION LIST

1. Research contained within this thesis

Cox, W. R., Dobbelaar, S., Meeter, M., Kindt, M., & van Ast, V. A. (2021). Episodic memory enhancement versus impairment is determined by contextual similarity across events. *Proceedings of the National Academy of Sciences U.S.A., 118*(48), e2101509118.

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Cox, W. R., Faliagkas, L., Besseling, A., van der Loo, R., Spijker, S., Kindt, M., & Rao-Ruiz, P. (in press). Interfering with contextual fear memories by post-reactivation administration of propranolol in mice: a series of null findings. Frontiers in Behavioral Neuroscience.

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3 In accordance with "CRediT": https://www.elsevier.com/authors/policies-and-guidelines/credit-author-statement

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2. Other publications

Cox, W. R., & Kindt, M. (2020). Aan exposure voorbij: farmacologisch versterken van extinctiegeheugen of verzwakken van angstgeheugen. In A. Greeven & A. A. P. van Emmerik (Eds.), *Handboek Exposure* (pp. 282-304). Boom uitgevers Amsterdam.

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