Fighting against fear

Novel approaches to understanding, modifying, and manipulating maladaptive memories

Elsey, J.W.B.

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Chapter 1.

General Introduction

Our genes encode the history of our ancestral environments, and equip us with adaptations to the general niche we can expect to inhabit as human beings. These adaptations develop over millennia. Our environments are far more complex, ever changing, and diverse across individuals and times than can be captured by species-wide genetic information and the reflexes they encode. It is our brains, and their capacity to store information acquired from experience, that enable us to survive, adapt, and thrive. Without this ability to form memories, we would be forever as newborn children, helpless and dependent.

Yet, when most people think of memory, they imagine the purposeful recollection of past events, or nuisances such as forgetting the location of their keys. Memory is much more than this. Far from a mere file drawer in which past experiences are stowed away for later consideration, memory is ubiquitous in our daily functioning and an integral guide to ongoing behavior and future plans. Without memory, we could not speak, for we must first acquire a language. We could not even understand other people's words nor the boundaries between them, as without experience and its storage as memory, spoken sentences are a largely uninterrupted stream of strange noises. We could not ride a bike nor drive a car, for these are motor skills we acquire through experience. We would not know where we are going nor what we are doing in any given moment, as this requires the continued reliance upon a stored representation of one's goals and how to achieve them. Finally, our emotional lives would be reduced to moment-to-moment sense impressions, with no means of differentiating those we deeply love, nor those we most fear, from a stranger.

This emotional dimension of memory has become a central focus of research into novel treatments and theories of a range of mental health conditions, from anxiety disorders and post-traumatic stress disorder (PTSD) to addiction. Key to these lines of inquiry is a distinction between adaptive and maladaptive memory, and a parallel can again be made to the information we store in our genes. What evolution has encoded in our genes is not always optimal (consider the blind spot that can be leveraged to produce an illusion on the cover page – it is an accident of the evolutionary trajectory of the mammalian eye that has produced this suboptimal 'design', which cannot now be undone). Likewise, not everything stored in memory is optimal or even accurate. Forming a representation of spiders as somewhat threatening may be of little consequence, but with avoidance and an increasingly

distorted sense of threat that develops over time, a pathological fear may develop. Just as with the blind spot, this developmental trajectory cannot simply be reversed.

In addition, some adaptations may have been entirely appropriate in a particular context, but become maladaptive when retained under changing environments (e.g., our predilection for high calorie foods, which served us well when food was scarce, but can be a burden in the age of fast food). It is just so with memory. Having experienced a violent assault, for example, it is wise to pay close attention to predictors of similar threats, avoid certain places, and be vigilant when in similar environments. Those suffering from PTSD, however, appear unable to regulate this otherwise adaptive threat response system to fit the context, resulting in intense stress and nightmares even when the sufferer is objectively safe.

Maladaptive memory has thus become a major therapeutic target. For example, exposure is a technique commonly used in the treatment of anxiety disorders, in which patients are confronted with their fears (McNally, 2007; Powers & Emmelkamp, 2008). This line of treatment developed out of basic studies of learning in animals. Animals that had been taught to fear a particular stimulus by pairing it with an aversive event (conditioning/acquisition) could be made to display less fearful responding by re-exposing them to the newly feared stimulus in the absence of the aversive event (extinction). Likewise, patients can be made less fearful of feared objects or situations through exposure to them in the absence of negative outcomes. Yet, research in animal models of learning has indicated that extinction training does not cause unlearning of the original fear memory, but rather creates a new memory trace that competes with originally learned information for control over behavior (Bouton, 2002). Aversive experiences, changes in context, or the simple passage of time can lead to the resurgence of behavior tied to the original memory trace. As the underlying mechanisms of change are thought to be analogous in exposure therapy, such findings help explain relapse in clinical settings. More intriguingly, they also point to ways of improving treatment outcomes. Clinically oriented researchers such as Bouton (2002), Brewin (2006), and Craske et al. (2014), now emphasize that both cognitive and behavioral treatments should focus on the generation of alternative adaptive memories, which can compete with (and hopefully beat) maladaptive representations for retrieval. A variety of techniques for maximizing the power of these competing memory traces are now the subject of intensive translational research.

Developments in our understanding of the neurobiological basis of memory have also opened up novel pharmacological approaches to the prevention and treatment of disorders with a basis in maladaptive memory. Firstly, it is now understood that adrenal stress hormones/neurotransmitters released during and after traumatic experiences can have profound effects upon memory strength in both humans and animals (Cahill & Alkire, 2003; McGaugh & Roozendaal, 2002; Soeter & Kindt, 2012b). As will be considered in Chapter 2, this release of hormones/neurotransmitters may be at the core of the recalcitrant and disturbing memories that underpin PTSD. It may be possible to administer drugs that block their effects, preventing the development of an 'over-consolidated' memory for the traumatic event (Pitman, 1989; Pitman & Delahanty, 2005). This approach cannot be utilized for the bulk of mental health disturbances: It may be difficult to identify problematic learning experiences in real time, there is little ability (or inclination) to rapidly administer prophylactic interventions even if this could be done, and such approaches would not be applicable to people who already have PTSD. Here too, developments in our understanding of memory formation and malleability may prove informative.

The dominant model of memory formation proposes that memories transition from a short-term and relatively unstable trace to a more persistent, long-term form (McGaugh, 2000). This transition from short-term memory to long-term memory is known as consolidation, and is most commonly thought to be mediated by protein synthesis dependent synaptic plasticity (Kandel, Dudai, & Mayford, 2014). Protein synthesis inhibitors (PSIs) can prevent the expression of long-term memory when administered shortly after learning (Schafe & LeDoux, 2000). Once consolidated, memories appear insensitive to protein synthesis inhibition, and can prove highly resistant to attempts at modification (LeDoux, Romanski, & Xagoraris, 1989). While there remain doubts among some researchers about the necessity of *de novo* protein synthesis in long-term memory formation (Gold, 2017), the synaptic plasticity that such protein synthesis is held to support certainly seems integral to normal memory functioning.

Even though long-term memories may be relatively insensitive to interference, it has been found that reactivation of a memory can render it vulnerable to amnestic interventions once more: protein synthesis inhibition shortly after *reactivation* can prevent the later expression of long-term memory (Nader, Schafe, & LeDoux, 2000).

Other drugs (such as propranolol) may also produce memory disturbances when administered after reactivation (Dębiec & LeDoux, 2004; Przybyslawski, Roullet, & Sara, 1999). Through blockade of g-protein coupled receptors (namely beta-adrenergic receptors), propranolol is thought to interfere with molecular cascades in the adenylyl cyclase pathway that can ultimately result in the activation of important cAMP response element binding (CREB) proteins, which regulate gene transcription and play important roles in synaptic plasticity (Kandel, 2012; Przybyslawski et al., 1999).

It is now suggested that, under certain conditions, a consolidated memory can be brought into a temporary, labile state by reactivation, requiring restabilization in a manner similar to consolidation in order to persist. Due to parallels with initial consolidation, this process has become known as reconsolidation (Nader & Hardt, 2009; Przybyslawski & Sara, 1997). Once labilized, it may be possible to modify the memory, or disrupt its restabilization. If maladaptive memories do indeed underpin many psychiatric conditions, then the capacity to modify or manipulate them would provide a significant breakthrough for clinical science, potentially opening the door to rapid and long-lasting improvements in symptoms without extensive psychological therapy or continual drug use (Elsey & Kindt, 2017b).

Research into the prospects of harnessing novel insights into the manipulation and modification of memory is, however, in its infancy. At the time of my arrival at what has now become the *Amsterdam Emotional Memory Lab*, studies investigating the use of pharmacological agents to interfere with memory in humans were, in particular, quite few and far between. As these studies are reviewed extensively in Chapters 2 and 5, I will only mention them briefly here. Building upon considerable bodies of research in animal models, studies aimed at pharmacologically interfering with consolidation in humans stood at two extremes. On the one hand, there were multiple studies investigating propranolol's effects on emotionally tinged declarative memories, which found that propranolol could reduce the typical enhancement of memory associated with emotional items (Lonergan, Olivera-Figueroa, Pitman, & Brunet, 2013). However, almost all involved drug administration before the learning experience, limiting their translational relevance for PTSD. On the other hand, studies of propranolol's effects in actual trauma victims showed mixed efficacy of post-trauma propranolol, but were plagued by practical difficulties for drug administration within a theoretically optimal time post-trauma (e.g., Stein, Kerridge, Dimsdale, &

Hoyt, 2007). Hence, there was space for translationally informative research that stood between these two poles.

Research into the pharmacological modification of *existing* emotional memories stood at a crossroads, aiming to move from powerful effects observed in experimental studies to interventions in subclinical and clinical populations. While some early reconsolidation work in humans had already investigated the possibility of ameliorating PTSD symptoms with memory reactivation + propranolol (e.g., Brunet et al., 2008), the approach of Prof. Kindt at the *Amsterdam Emotional Memory Lab* was somewhat different. This approach involved first aiming to closely approximate successful studies of reconsolidation in rodents by utilizing fear conditioning in humans. Kindt, Soeter, and Vervliet (2009) demonstrated that fear-potentiated startle responses to a stimulus that had been paired with shock during the acquisition phase of conditioning could be neutralized by administering propranolol, timed to coincide with memory reactivation and the hypothesized process of post-reactivation reconsolidation. Moreover, unlike merely extinguished memories, this conditioned responding did not return after presentation of further unpaired shocks. Multiple studies building upon these initial findings aimed to investigate boundary conditions for producing the amnestic effect (Sevenster, Beckers, & Kindt, 2012b, 2013, 2014b), what sort of reactivation cues were necessary (Soeter & Kindt, 2015b) and the specificity of the effects (Soeter & Kindt, 2011), among other results (all reviewed in Chapter 5). These findings were intended to inform as to the possibility and optimal means of interfering with a clinically relevant and naturally occurring fear, a possibility that was demonstrated through a successful reconsolidation-based treatment for fear of spiders (Soeter & Kindt, 2015a). A number of translational research questions could still be answered using fear conditioning, and the extension of reconsolidation-based interventions to other fears remained an untapped possibility.

Outline of the dissertation

At this point in a dissertation, it is usual to explain how a completely logical and coherent plan threads together the studies contained within. The reader will likely note that the three empirical studies selected for inclusion in this thesis are in some ways quite far removed from one another. One experiment involves the blockade of *con*solidation in a laboratory model of traumatic memories. Another involves investigating whether a *re*consolidation-based intervention can prove fruitful in

tackling fear of public speaking. A final series of experiments investigates the nature of beliefs in individuals with and without fear of spiders. This diversity of content reflects both the tremendous freedom granted to me by my supervisor (Merel Kindt), and the frustrations of executing what at first seemed a reasonable and achievable plan but turned out to be far trickier. Although we began with a logical series of experiments – each building from one to another – primarily involving fear conditioning and then extending insights from the anticipated findings into clinical interventions, I experienced considerable difficulties with even some quite simple achievements (e.g., getting unambiguous differentiation of participants' responses to stimuli that predicted shocks vs. those that did not!).

Though certainly frustrating, these setbacks prompted consideration of other informative paradigms, or even designing wholly new experimental setups. In addition, our focus switched quite quickly to investigating reconsolidation-based approaches directly in clinical patients and subclinical populations, providing firsthand experience both of the difficult but essential process of the later stages of clinical translation, the nature of the mental health problems we are trying to treat, and the sometimes-extraordinary power of the phenomenon we have been trying to harness. As an example of this clinical and patient-focused work, committee members are invited to visit the private web link they have received, where I am temporarily hosting a video demonstration of a reconsolidation-based intervention for a real arachnophobic patient. The video shows how a very brief reactivation of a patient's fear, followed by propranolol administration, can result in dramatic changes in behavior and attitudes towards the patient's feared stimulus. Experiences such as these ultimately provided impetus not only to try to expand the applicability of reconsolidation-based approaches to other fears (Chapter 4), but for what I hope can develop into clinically-relevant research with implications beyond reconsolidation (Chapter 6).

I would nevertheless propose two threads that weave their way through this dissertation, and my efforts throughout my PhD. Firstly, the push to get closer and closer to the legitimate clinical phenomena we ultimately aim to understand or tackle, while trying to retain experimental control, such that we can make clear inferences while maintaining clinical relevance. Chapter 2 thus represents the use of the 'trauma film paradigm', which was intended as a means of reducing the gap between research demonstrating that emotionally valenced stories can be affected by propranolol

administration, and the secondary prevention of PTSD that these studies are held to inform. Chapter 4 is a systematic, placebo-controlled pilot study of the use of propranolol in the reduction of a naturally occurring social fear, which would represent a substantial expansion of the capabilities of reconsolidation-based interventions that have currently shown most efficacy in relatively simple fears and phobias. Finally, Chapter 6 investigates the nature of beliefs among fearful individuals, and aims at developing a more nuanced understanding of anxiety-related beliefs that may inform approaches to treatment, and perhaps how we understand beliefs across a range of disorders. This research developed directly out of a desire to understand the sometimes dramatic changes that could be produced in patients through reconsolidation-based interventions, and the disconnects between patients' feelings and beliefs. In Chapter 3, I also consider ethical objections or considerations for the use of reconsolidation-based procedures, which I hope can help frame an empirically informed discussion should reconsolidation ultimately be incorporated into standard practice. Furthermore, in the extensive review of human reconsolidation research that forms Chapter 5, in addition to taking a fine-toothed comb to the reconsolidation literature, I urged researchers to unite around the goal of producing clinically informative studies, and ultimately realizing the clinical potential of reconsolidation.

Secondly, the studies all focus on emotional memory, and the ways in which memory may or may not be modifiable, vulnerable to interference, or resistant to certain means of intervention. The term memory is construed broadly to encompass a range of mental representations people hold with regards to past experience, and which inform their future behavior. Chapters 2 and 4 focus on the pharmacological manipulation of initial memory formation, and the modification of long-term memory traces, respectively. Chapter 6 focuses on the nature of irrational belief, and the possibility of more emotional vs. logical representations that individuals with fears and phobias may hold.

In the final Discussion (Chapter 7), I try to bring these emphases on clinical relevance and memory manipulation together, with consideration of some difficult issues that may need to be addressed on the way to realizing the clinical potential of reconsolidation-based approaches. I also consider to what degree these studies, and the wider developments in pharmacological memory manipulation and advances in

psychotherapy, can be incorporated into a contemporary understanding of the goals of therapy and mechanisms of change.

A final note to the intrepid reader: Those who have agreed (or been compelled) to read this dissertation may note with some concern the length of certain sections of it, most notably Chapter 5. In the interest of preventing any aversive memories, I would like to now highlight that a large number of those pages are tables detailing the studies described in the text – a useful reference for researchers, but the current reader may happily find that they can sail over several such tables and make considerable headway with the text by doing so. If all else fails, you may find your own means of pharmacological manipulation available at the local wine store, to accompany the reading.