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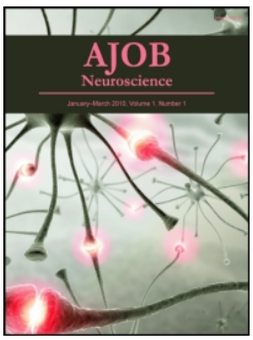

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Target Article

Manipulating Human Memory Through Reconsolidation: Ethical Implications of a New Therapeutic Approach

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Memories are fundamental to human experience: We are in many ways the products of our pasts, recorded in memory. The influence of memory over current experience is both a blessing and a curse, for just as we find solace in the remembrance of times past, we may also be plagued by pathological memories. Such maladaptive memories are a core feature of several psychiatric conditions, from anxiety disorders to addiction. In this article we present work from our own lab and others that shows the remarkable malleability of human memory, and how the disruption of maladaptive memory reconsolidation is being used for therapeutic purposes. If bioethical concerns about memory modification are to be more than purely hypothetical considerations for the future, they should be grounded in cutting-edge contemporary research. We provide the necessary overview of the field, then raise, challenge, and discuss several old and new ethical concerns.

Keywords: emotion, enhancement, memory, neuroscience, psychiatric disorders, posttraumatic stress disorder

Advances in brain science provide increasingly powerful ways of manipulating the processes that underpin memory. These developing capacities hold great therapeutic potential, as disruptive or maladaptive emotional memories appear to be a crucial component in the development and maintenance of numerous psychiatric disorders (Ehlers and Clark 2000; Hyman, Malenka, and Nestler 2006; Ledoux and Muller 1997). However, our memories also form the foundation of our identities. It is not surprising, therefore, that debates have arisen regarding the ethical implications of memory modification. Psychological therapies routinely affect memories (Brewin 2006), and in daily life we continually recall, update, and generate new memories. Nevertheless, novel combinations of behavioral and pharmacological interventions with the potential to precisely target and modify memories have generated considerable debate.

Early considerations of the ethical implications of pharmacologically aided memory modification (e.g., President's Council on Bioethics 2003; Kolber 2006; Henry, Fishman, and Youngner 2007) primarily focused on research demonstrating that drugs could be administered in the aftermath of trauma to block the initial storage or "consolidation" of traumatic memories, thereby preventing the development of posttraumatic stress disorder (PTSD) (Pitman et al. 2002; Vaiva et al. 2003). However, prophylactic uses of drugs in PTSD are not the only therapeutic path down which research on memory has lead in recent years.

The discovery and use of a reconsolidation-based therapeutic approach is a truly significant development upon previous work on memory consolidation. A consolidation-based approach relies on an intervention occurring within a few hours of an event that is expected to lead to psychological problems, whereas with a reconsolidation-based approach a maladaptive memory might conceivably be reactivated and disrupted at any time. Even in PTSD, in which one can pinpoint specific causal events that lead to the disorder, intervening within the specific time window of consolidation is challenging at a practical level and, as discussed later, raises several ethical concerns that cannot be leveled at a reconsolidation-based approach. Most strikingly, several disorders appear to have maladaptive emotional memories as a core feature and yet have no clear antecedent event leading to their development, making a consolidation-based approach impossible. Hence, the scope of application for reconsolidation-based treatments

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is much broader than for consolidation-based ones, and the possible ethical implications are accordingly wider.

A key aspect of bioethical discussion around such developments is the anticipation of ethically relevant future scenarios. However, such considerations reflect assumptions about what is or is not possible, and empirical research can help elucidate which of these scenarios are more or less likely. Hence, if bioethical considerations are to be more than purely hypothetical considerations for the future, they might best be grounded in cutting-edge research.

In this article, we aim to provide an overview of the key developments in reconsolidation-based memory manipulation from which ethical discussion could proceed. We present experimental work on modifying memories by disrupting the process of memory reconsolidation, highlight its clinical applications, and challenge several ethical concerns that have been raised in relation to such interventions. We then discuss some novel ethical issues regarding the use of reconsolidation-based approaches beyond therapy. Due to space limitations, we emphasize the combination of behavioral and pharmacological intervention that has been the focus of our lab, and particularly the use of the noradrenergic beta-blocker propranolol. Alternative drugs or purely behavioral interventions may nevertheless be promising avenues for therapeutic interventions.

MEMORY RECONSOLIDATION—EXPERIMENTAL WORK

We do not remember everything we experience. Research shows that upon encountering new information or experiences, we form a short-term memory that is labile and vulnerable to interference (Lechner, Squire, and Byrne 1999; McGaugh 2000). Consolidation refers to the process by which some information from short-term memory is stored more stably in long-term memory (Lechner et al. 1999; McGaugh 2000). At the neurobiological level, this development of a long-term memory trace is mediated by protein synthesis, the inhibition of which prevents the expression of long-term but not short-term memory (Schafe and LeDoux 2000). Presumably, protein synthesis is required to induce lasting structural changes in neurons and/or connections between them, thereby creating a more stable neural network that represents the memory in the brain (Kandel, Dudai, and Mayford 2014).

Crucially for the prospect of reconsolidation-based memory modification, long-term memory traces are not immutable. Consolidated memories can, under certain conditions (Alfei et al. 2015; Sevenster, Beckers, and Kindt 2013), become malleable after reactivation, and require further protein synthesis in order to be restabilized. This was first convincingly demonstrated by Nader, Schafe and LeDoux (2000) in a rodent model of fear learning known as auditory fear conditioning. During auditory fear conditioning, rats are exposed to a tone that is followed by an electric shock. Rats develop a defensive freezing response to this tone because of the learned association between hearing the tone and receiving the shock. This freezing response serves as an index of fear memory. Just as the initial long-term storage of a memory was found to depend on protein synthesis within a specific time window from learning, Nader and colleagues found that long-term memory could also be blocked if they inhibited protein synthesis in the amygdala shortly, but not 6 hours, after the reactivation of a memory for auditory fear conditioning. Inhibition of protein synthesis did not prevent the short-term expression of the fear memory: 4 hours after protein synthesis the rats still froze in response to the tone that had been paired with shock. However, 24 hours later this learned freezing response was absent. Due to similarities with initial consolidation, this process has become known as *reconsolidation* (Nader and Hardt 2009).

Reconsolidation appears to open a window during which the content of the reactivated memory can be edited (Redondo et al. 2014), or its reconsolidation into long-term memory blocked or disrupted, potentially inducing memory loss or modification (Nader 2003). The induction of memory changes after the disruption of reconsolidation using a range of memory-modifying agents has now been found in model organisms ranging from fish to crabs to rats (Eisenberg, Kobilo, Berman, and Dudai 2003; Nader et al. 2000; Pedreira, Perez-Cuesta, and Maldonado 2002). More recently, experimental work has demonstrated reconsolidation-based memory modification in humans (Kindt, Soeter, and Vervliet 2009; Sevenster, Beckers, and Kindt 2013; Soeter and Kindt 2012).

The beta-blocker propranolol has shown particular utility in reconsolidation studies with human subjects. Propranolol has previously been thought somewhat useful for its general anxiolytic properties, such as the reduction of tremor during stressful performances. These properties appear irrelevant to its memory-modifying potential, given that beta-adrenergic drugs without memory reactivation (Kindt et al. 2009, Soeter and Kindt 2010) do not have a long-term fear-reducing effect. In addition, a beta-adrenergic blocker with the same properties but that does not cross the blood–brain barrier has no such effects (Kindt and Soeter 2016). Instead, propranolol appears to exert its influence on memory through indirect interference with protein synthesis, via the blockade of beta-adrenergic receptors in brain regions involved in memory storage.

Several studies in humans have demonstrated that the administration of propranolol before or immediately after the reactivation of a conditioned fear memory modifies the memory trace (Kindt et al. 2009; Soeter and Kindt 2011; multiple studies reviewed in Kindt 2014). Participants in such experiments still remember the previously learned contingency between stimuli and shocks. However, after disruption of reconsolidation their startle responses to danger stimuli, which are normally potentiated, return to the level of a stimulus never paired with shock (Soeter and Kindt 2011). As startle responses appear to reflect the emotional valence of a stimulus (Lang, Bradley, and Cuthbert 1990), it seems that reconsolidation blockade with propranolol neutralizes the negative emotional valence transferred to the danger stimulus during learning.

Crucially for the demonstration of a reconsolidation effect, reactivation followed by placebo does not induce changes in the memory, nor does the administration of propranolol in the absence of memory reactivation. Moreover, in the hours following the memory-modifying intervention, the startle response remains potentiated, reflecting the retention of a short-term memory trace (Nader et al. 2000; Kindt and Soeter 2016). Similarly to animal studies, prediction error—operationalized as a difference between what was predicted and the actual situation—appears to be required to elicit reconsolidation, as propranolol or other memory-altering drugs do not affect the memory without a violation of previously acquired expectations (Alfei et al. 2015; Morris et al. 2006; Pedreira, Perez-Cuesta, and Maldonado 2004; Sevenster et al. 2013). These findings form a convincing case for the occurrence of reconsolidation in humans and the possibility of its disruption.

MEMORY RECONSOLIDATION—CLINICAL APPLICATIONS

The discovery that already consolidated memories can be rendered vulnerable to disruption after reactivation opens the possibility of using this approach to target pathological memories. A number of disorders seem to have maladaptive emotional memories as a core feature. For example, it has been suggested that fear in specific phobias is derived from learning either directly, through observation, or from information, that certain animals, objects, or situations are particularly dangerous or otherwise unpleasant (Rachman 1977). PTSD is another disorder in which maladaptive emotional memories and memory disturbances play a key role. These can include intrusive imagery related to the event, as well as surges of intense emotion triggered by trauma reminders (Ehlers and Clark 2000a). PTSD is a complex disorder in which several factors beyond fear are implicated, but symptoms such as hypervigilance and avoidance clearly demonstrate the major involvement of fear memories.

Where stimuli pose legitimate threat, fear is both adaptive and rational. In contrast, phobic fear responses are grossly out of proportion to danger. Hence, activation of phobic fear memories can greatly restrict a person's everyday functioning without benefit. Similarly, it is rational to remember what happened to one in order to learn for the future, and to avoid situations related to a traumatic experience if these predict further harm. It is also not a sign of ill health to be distressed, or even deeply troubled, by tragic events (Parens, 2010). In PTSD, however, memories related to a traumatic event become highly disruptive, being triggered seemingly out of nowhere and difficult to keep out of mind even in safe situations. In severe cases, trauma memories so vividly keep the threat alive that patients act and feel as if they are actually still in the traumatic situation. Successful modification of such memories through a reconsolidation-based intervention could significantly improve the lives of those suffering from such disorders.

Propranolol administration after the retrieval of traumatic memories could interfere with trauma memory reconsolidation, just as immediate posttrauma propranolol administration might interfere with their consolidation (Pitman et al. 2002; Vaiva et al. 2003). Brunet and colleagues (2008) asked patients with chronic PTSD to recount their traumatic experiences, and then gave them propranolol (placebo controlled, double-blind).[1] One week later, patients returned to the lab and listened to imagery scripts based upon the traumas they had recounted in their first sessions. Physiological responses to these scripts were significantly lower in the patients treated with propranolol relative to placebo, and had in some cases dropped below previously defined PTSD cutoffs.

Brunet's research group has also explored the use of multiple reactivation sessions. In three open-label trials, patients underwent six weekly trauma recall sessions under the influence of propranolol (Brunet et al. 2011). By session five, patients' symptoms were below the cutoff for PTSD. Neither the type of trauma nor the time elapsed since it occurred was found to affect treatment outcomes, although the treatment was more effective for women than men (Poundja, Sanche, Tremblay, and Brunet 2012). This may prove important, as one study that failed to find a reduction in psychophysiological responding after reactivation with propranolol had only male participants (Wood et al. 2015).

These findings provide support for the idea that propranolol administered so as to interfere with the reconsolidation of a reactivated trauma memory could significantly reduce symptoms of PTSD. A large, randomized controlled trial with participants representing both genders and a range of PTSD etiologies would help assess the viability of such a treatment, but the current results are very promising.

Research into the therapeutic applications of reconsolidation-based memory modification is not restricted to PTSD. Building upon our laboratory work showing that fear responses to specific stimuli could be reduced through the disruption of reconsolidation, we tested whether such an intervention might prove useful in treating specific phobias.

We selected 45 individuals who were highly fearful of spiders, scoring above the cutoff for arachnophobia on questionnaire measures and demonstrating marked aversion to a real-life spider (Soeter and Kindt 2015). Participants were split into 3 groups of 15. During the intervention phase, one group received only propranolol to test for nonspecific effects of the drug on spider fear. The remaining participants were exposed

1. Brunet and colleagues have since switched to a procedure in which propranolol is administered before reactivation, to allow for peak bioavailability to be reached closer to memory retrieval (Brunet et al. 2011). Strictly, such a design cannot rule out an effect other than reconsolidation such as interference with recall. However, such alternative explanations may not be the most reasonable, given that recall appears to be undisturbed in this and other studies that utilized pre-reactivation propranolol (Kindt, Soeter, and Vervliet 2009), and what this interference effect would actually be has also not been explained.

to a live tarantula to reactivate their fear, and then received propranolol or placebo, double blind. Four days later, the participants were again exposed to the tarantula and were asked to touch it. Strikingly, almost every participant in the active treatment group (reactivation + propranolol) was able to touch the tarantula, compared with almost no participants in either of the inactive treatment groups. None of the participants had been able to touch even a smaller tarantula before treatment. Those who received active treatment also reported less subjective anxiety when confronted with the tarantula than on the treatment day, whereas there was no change in the placebo group. Participants were then followed up approximately 2 weeks, then 3 months, and finally 1 year after treatment to undergo behavioral approach tests with the smaller, faster moving tarantula. Again, participants in the active treatment group were able to touch or even hold this smaller tarantula and maintained this ability at the 1-year follow-up. Behavioral changes in relation to a spider that was not used in the treatment session suggest that the reduction in fear generalized from the specific tarantula used to reactivate the participants' fear, a possibility that is further supported by questionnaire scores about spiders in general, and behaviors around them, also dropping to below a phobic cutoff score in the active treatment group. In comparison with this rapid transformation of behavior in the active treatment group, behavioral approach scores in the inactive groups remained low all the way up to the 1-year follow-up.

These findings indicate that the behavioral tendency associated with a specific fear can be rapidly transformed through the disruption of fear memory reconsolidation, with concomitant changes in phobia-related cognitions, and that the changes associated with the abrupt transformation last for at least one year. Crucially, we demonstrated that this was neither a pure drug nor a pure exposure effect: The combination of memory reactivation and propranolol was required to see any benefit. Since this study, we have found similar effects in a range of other specific phobias, including fear of snakes and fear of heights.

Given these results, it is clear that even very old and strong memories can be modified through reconsolidation, as many participants could not think of a time when they had not had their fear. Though tentative, one inference is that other anxiety disorders with a chronic course that have more deleterious effects on everyday functioning might be treated with a similar approach. Further studies are required (and are underway) to assess the viability of such interventions, but preliminary results give reason for optimism.

RECONSOLIDATION-BASED MEMORY MODIFICATION IN LIGHT OF CONSOLIDATION

In the previous section, we showed that the prospect of disrupting reconsolidation in order to modify memories has great therapeutic potential. However, a number of concerns have been raised regarding memory-modifying procedures. Before considering some of these that might relate to a reconsolidation-based approach, it should be noted that a number of objections leveled against the use of propranolol to interfere with the consolidation of traumatic memories do not apply to the reconsolidation-based treatment of PTSD. Given the similarity of administering propranolol in the consolidation window to its administration in the reconsolidation window, it is worth making this explicit.

First, reconsolidation-based treatments negate concerns over who should receive propranolol in the immediate aftermath of trauma, as they would only take place after the development of PTSD. There would also be ample opportunity for recovery from trauma and positive "posttraumatic growth" to materialize under such circumstances (cf. Warnick [2007]—though Warnick does not provide direct evidence that growth could not occur even with a consolidation-based intervention). Given that only those with a maladaptive response to trauma would receive treatment, this would also guard against pathologizing bad memories and experiences per se, an issue raised by Bell (2007). Additionally, neither trauma survivors nor their families would be required to make a decision about treatment in a compromised state shortly after trauma.

This does not mean that reconsolidation-based approaches are strictly preferable to effective consolidation-based ones, but they do appear to nullify several ethical concerns. Researchers should nevertheless continue to investigate prognostic indicators that might better predict those most likely to develop PTSD (Ozer, Best, Lipsey, and Weiss 2008). If powerful predictors are discovered, then exceptionally high-risk individuals could be offered a consolidation-based intervention, whereas a reconsolidation-based treatment might be preferred for those of lower risk.

ETHICAL CONCERNS OVER RECONSOLIDATION-BASED MEMORY MODIFICATION

Despite relative immunity to some objections leveled against consolidation-based treatments, reconsolidation-based approaches may still be subject to several concerns regarding memory-modifying pharmacological approaches. These include the accidental modification or erasure of the wrong memories, the loss of autobiographical memories about events, and undesirable consequences of the loss of a memory's emotional valence. We aim to show that these issues represent empirical claims about the nature of treatment that can be shown to give little cause for concern in light of contemporary research. While laboratory research is subject to limitations such as its generalizability to clinical settings or other real-world applications, findings in clinical samples discussed in the following also support our position. In any case, we would argue that such lab work provides a surer footing from which to judge the most important bioethical concerns than pure intuition or imagination.

Findings from our lab suggest that interfering with the wrong memories is unlikely. In one study, we taught participants to associate two different stimuli with electrical shocks and a third stimulus with safety on the first day of training (Soeter and Kindt 2011). On day 2, we gave participants propranolol and reactivated just one of their memories for a shock stimulus by presenting it without any shock. On day 3, participants returned and we tested their responses to all three stimuli. Startle responses to the reactivated stimulus were selectively abolished, with responses to the unreactivated stimulus left intact. Hence, even when stimuli are learned under identical circumstances and at the same time, it is possible to disrupt just one.

In addition, mere reactivation is not enough to render a memory vulnerable to reconsolidation blockade. Several studies suggest that prediction error or novelty detection—that is, a learning event in which one's expectations are violated, such as when a shock does not follow a stimulus consistently paired with shock in the past—is necessary to destabilize the memory (Alfei et al. 2015; Exotn-McGuinness, Lee, and Reichelt 2015; Morris et al. 2006; Sevenster et al. 2013). Given that reconsolidation-based memory modification depends upon specific requirements, the possibility of accidentally erasing the wrong memory should be low provided that sensible and careful reactivation procedures are used.

The loss of explicit, declarative, or autobiographical memory (i.e., those types of memory that refer to facts and events) from this procedure also seems very unlikely. Across all the studies in our lab, we have consistently found that conscious awareness of the previously learned contingencies was preserved after disruption of the learned fear response by propranolol (Soeter and Kindt 2010; Soeter and Kindt 2013). Rather than inducing complete amnesia for what is learned, administration of propranolol after memory reactivation seems to neutralize the valence transferred to the danger stimulus. Similarly, we found that arachnophobic participants had not forgotten their experiences with spiders, nor that they used to be afraid, following the disruption of fear memory reconsolidation (Soeter and Kindt 2015). Participants expressed the same explicit phobic belief system they held before the intervention, and it took several months before these cognitions fell in line with their abrupt change in behavior.

Likewise, the aim of reconsolidation-based memory modification in PTSD is not to make the patient forget the trauma. Rather, we aim to reduce the excessive emotional charge of the memory that may otherwise make the trauma very difficult to integrate and place in context (Brewin, Dalgleish, and Joseph 1996). As suggested by the President's Council on Bioethics (2003), total amnesia for a traumatic event would probably be undesirable, as memories of even very negative events might contribute to a person's understanding of his or her life and identity. However, individuals with PTSD are demonstrably struggling to achieve this level of adaptation, and although PTSD is characterized by intrusions from overly strong memories, it is generally not paralleled by enhanced declarative memory for the traumatic experience. Those suffering from PTSD often have impaired declarative memories for what happened to them and struggle with intentional recollection (Ehlers and Clark 2000; Samuelson 2011). Excessive emotional memories are an important factor that can hinder the patient's ability to recollect and understand what happened to him or her (Brewin et al. 1996; Ehlers and Clark 2000). Far from preventing the patient from incorporating the experience into a meaningful life story, a reconsolidation-based reduction in the emotional strength of poorly elaborated but intense emotional memories might even facilitate controlled recollection of trauma, aiding its integration into a coherent personal narrative.

Although previous studies investigating the effects of propranolol in combination with traumatic memory reactivation did not explicitly assess declarative memory, Brunet (cited in Villain et al. 2016) has noted that patients remembered their traumatic experience well even when required to generate their trauma script from scratch. Work in our lab also suggests that patients retain their autobiographical memories for what they feared. Although future studies might consider assessing any changes in declarative/autobiographical memory more precisely, serious concern over declarative amnesia seems unfounded.

Some purely behavioral interventions have demonstrated the possibility of impairing declarative memory for material learnt in an experimental setting (Forcato, Rodríguez, Pedreira, and Maldonado 2010; Forcato et al. 2007). However, successfully inducing impairment of declarative memories in studies such as these appears to rely upon the delivery of incorrect or altered information regarding the original learning material (Chan and LaPaglia 2013). When participants had their memories for previously learned material reactivated and were then given unrelated information to learn, there was no effect on their memory for the previously learned material. Hence, it has been suggested that this need to specifically target memories with misinformation could be a reason why drugs such as propranolol have not been found to interfere with declarative memories (Chan and LaPaglia 2013). Those concerned about the potential for reconsolidation-based (and consolidation-based) memory modification to interfere with autobiographical memory, and particularly eyewitness testimony, might more fruitfully turn their attention toward postevent debriefing, as well as misleading questioning and cross-examinations, which are likely to have far greater effects on the reliability of memory than propranolol and are also far more pervasive (Loftus 1992).

Assuming that autobiographical memories remain intact following a reconsolidation-based memory modification, it is nevertheless possible that dampening or neutralizing the emotional component of a memory is ethically questionable. Kabasenche (2007) and Hurley (2007) have emphasized that emotions can reflect moral considerations. The suggestion of these authors seems to be that some important moral signal might be lost with the loss of our "natural" emotional reactions to traumatic

experiences. Research into psychopathy, in which emotional processing and the recognition of distress are compromised (Blair, Jones, Clark, and Smith 1997; Patrick 1994), also highlights the importance of affective reactions in moral judgments and the development of moral sentiments, and could be seen to support this supposition (Blair 1995; Koenigs, Kruepke, Zeier, and Newman 2012).

Emotions can indeed be indicators that something morally relevant is occurring, but excessive emotional reactions to trauma are neither necessary nor sufficient to establish a moral wrong. For example, the traumatization of a hostage is not needed to confirm that a hostage taker may have transgressed a moral boundary. Other traumas may be terrible accidents for which no one is morally culpable, regardless of a survivor's emotional response. Moreover, individuals suffering from PTSD often have a number of emotionally laden responses that would be faulty indicators of moral transgressions, such as guilt and unjustified self-blame for their victimization. Hence, although there may be moral consequences if emotional responses to wrongdoing were to be universally dulled, these reservations do not seem to apply to the treatment of PTSD.

Quelling the emotional memories of a trauma victim suffering from PTSD would not numb that person to the impact of future experiences either. We have shown experimentally that emotional responses can be relearned through experience even after reconsolidation-based memory modification (Soeter and Kindt 2011). What this shows is that reconsolidation-based treatments do not produce a general disruption of emotion or of learning capabilities. Rather, they target responses to internal and external cues that have become associated with excessive fear or traumatic experiences. Normal responses to experience are not hindered when excessive responses to past memory triggers have been eliminated. There is thus little reason to believe that such approaches would lead to any collective numbing of important emotional responses.

In summary, empirical findings shed light on a number of ethical concerns raised against memory modification. We argue that the probability of affecting the wrong memory, losing autobiographical memory, or missing out on morally relevant emotional responses is very low provided appropriate care is taken.

THE USE OF PHARMACOLOGICAL AGENTS

Beyond whether or not reconsolidation-based memory modification might produce the unwanted effects outlined in the previous section, another question is whether even successful treatment of anxiety disorders with such a method is desirable. For example, some have questioned whether such a "fundamentally pharmacological approach" to phobias and anxiety ought to be pursued at all (BBC News 2009). The idea here seems to be that one should not reduce a psychological problem to one of neurochemistry, and that doing so might fail to tackle some putative root cause.

Such a critique fails to recognize that any kind of psychological disorder is equally a disorder of the brain. This perspective does not deny wider societal influences on the development of psychological disorders; it simply states that to the extent that there are such societal factors, they can have no effect on a person's mental health except insofar as they affect that person's brain.[2] Even the most extreme event would have no impact on a person's mental health if it did not result in brain changes. Likewise, it should be recognized that all interventions, if they are to affect mental health, must produce changes in the brain.

Therefore, it is incorrect to rule out the use of pharmacological agents as inappropriate for treating psychological disorders in principle. This is not to say that pharmacological approaches are necessarily good, but merely that a mental disorder could be tackled by any approach that will ultimately affect its brain basis. This may be achieved through various means, including societal transformation, individual psychotherapy, or the aid of a pharmacological intervention. Whether one particular approach is more or less suitable for treating a disorder is both an empirical question (determined by whether such a treatment is more or less effective in treating the disorder in actuality) and a theoretical one (determined by whether the explanatory model underpinning the approach would lead one to expect it to be a more or less effective treatment).

With regard to psychological/behavioral therapies for anxiety disorders and phobias, there is evidence that cognitive behavioral therapy (CBT) can be effective (Butler, Chapman, Forman, and Beck 2006; Hofmann and Smits 2008). However, there is also room for improvement. A sizable proportion of patients do not benefit from such therapies, and among those who do benefit, only about 40% achieve sustained recovery, with the majority of patients (60%) showing relapse (Durham et al. 2012; Hofman and Smits 2008; Loerinc et al. 2015).

Theoretical models of the mechanisms of change in psychotherapy provide good explanations for why relapse might occur. Brewin's (2006) model of CBT suggests that therapy produces new memories and ways of thinking that compete with old ones for control over behavior and mood. It is always possible that old memories could regain their previous dominance because they are not necessarily directly modified by such treatments. Similarly, leading explanations of extinction learning (which provides the experimental basis for exposure therapy) propose that exposure to feared stimuli reduces anxiety by creating new memories that inhibit the old memory trace (Bouton and Swartzentruber 1991; Bouton, Westbrook, Corcoran, and Maren 2006; Craske et al. 2014). Again, relapse can be

2. Neither does such a view suppose that having removed the brain effect of such factors, one would not want to tackle systemic issues that may have led to them. Those who believe that such a perspective does entail this conclusion should understand that an individually based psychological treatment is as open to such a critique as an individually based pharmacological one.

understood as the resurgence of the old, maladaptive memory.

Psychotherapies are often contrasted with typical pharmacological approaches that are seen as purely palliative in nature and thus more prone to relapse (Hollon, Stewart, and Strunk 2006). This is because standard pharmacological treatments generally seek to redress a purported neurochemical imbalance through the delivery of the respective chemicals to the brain. Unless the source of this imbalance is addressed, one would not expect a person discontinuing such medication to be cured of his or her problems. Increased relapse rates following standard pharmacological treatments relative to effective psychotherapies are predictable from the explanatory models that underpin these treatments: In psychotherapy the patients take what they have learned with them, whereas in pharmacotherapy they cannot learn to summon the effects of a drug at will. If one couples this with the plethora of side effects that can accompany prolonged use of psychoactive medication, one might reasonably form the general impression that a purely psychological approach is preferable to a purely pharmacological one, and that pharmacological approaches do not tackle the core problems of the disorder. Nevertheless, it would not logically follow that any treatment involving a pharmacological agent is inappropriate, inferior to a psychological one, or only palliative. This would depend entirely on how the treatment actually works.

The reconsolidation-based memory modification approach that has been the focus of this article is very different from typical pharmacological treatments, and its proposed mechanisms—derived from neurobiological research in animal models—give reason to suspect that it may prove superior to standard pharmacological and psychotherapeutic approaches in at least some respects. Rather than a putative neurochemical imbalance, our basic model of this treatment for phobia argues that one highly important factor maintaining the disorder is the presence of a maladaptive fear memory, which causes the excessive provocation of fear and anxiety in response to particular stimuli. Reactivating this memory under specific conditions is proposed to trigger reconsolidation. A pharmacological agent that interferes with the process of reconsolidation is delivered to disrupt the reconsolidation of the maladaptive memory, thereby treating a key component of the disorder. In contrast to typical pharmacological treatments, the drug is not taken on a daily basis but only once, during a specific time window around memory reactivation, and the delivery of this drug in the absence of reactivation does not have—and theoretically is not expected to have—any lasting effect on psychopathology.

If this model is approximately accurate, one would expect such a treatment to result in less relapse than standard pharmacotherapy, and possibly even less than effective psychotherapies, because the core fear memory is supposedly changed as opposed to inhibited by new learning. Though further research needs to be conducted regarding the question of comparative effectiveness and longer term outcomes, our initial 1-year follow-up of those who received treatment for arachnophobia found no relapse. Looking at these empirical findings, and the theoretical model that underpins the various available treatments, it would be rash to dismiss this memory modification approach as in some way wrong due to involving a pharmacological component.

BETTER THAN WELL

So far, we have considered the use of reconsolidation-based memory modification in relation to the treatment of mental disorders. However, some anxiety disorders may differ from other clear-cut cases of medical illness, in which one can define illness as, for example, the presence of infection, and health as its absence. Many fears seem to lie on a spectrum, ranging from indifference all the way to terror and phobic responses. Because there is no single set of behaviors that is normal with regard to specific fears, but rather a broad spectrum that comes under the umbrella of normality, a reconsolidation-based treatment for specific phobia may not simply restore health, as does a course of antiviral medicine. Some patients receiving treatment may end up less fearful than some "normal" individuals. For example, we have observed patients want to pick up the tarantula or have it crawl up their arm. Many nonphobic people would refuse to do this. Hence, in some instances, we find previously phobic individuals becoming "better than well" (Elliott 2004). These individuals would still be defined as normal, but they are less fearful than the average normal person.[3]

This raises the question of how others will respond if those with a previously pathological fear come to be less fearful than them. Some may start to see their own "normal" fears as a burden that can be removed. This is a far-fetched concern for arachnophobia, but in some instances even small reductions in fear could lead to considerable personal gain. This is particularly the case with competitive professional sportspeople and musicians. Might a gymnast have some residual fears he or she feels prevent him or her from reaching a peak? Could years of practice on the violin be supplemented by a reconsolidation-based reduction in performance anxiety? Such interventions would be appealing if they gave the recipients an edge over the competition, enabled them to compete on level terms with those assumed to be already using them, or simply leveled the playing field with those who are constitutionally less anxious.

There is already a long-standing debate about the use of performance-enhancing drugs in sports (Fraleigh 1984). The use of anxiolytic drugs in professional musicians is also quite commonplace, and some already use

3. This level of change does not always occur. Also note that patients' confidence does not reach irrational nonchalance: They still appear to show totally appropriate fear responses if the spider makes a threat display.

propranolol (Kenny 2005), though not in a way that would trigger memory modification. If the principal concern over the use of such drugs outside the traditional remit of therapy is the long-term health of the user, then a single dose of propranolol in a reconsolidation-based intervention is preferable to repeated consumption at each performance. However, as with other performance enhancements, there are wider considerations, such as unequal access to treatment or interference with the "natural" limits of human performance. If the use of such interventions is permitted, those who refuse or are unable to utilize such treatments (e.g., for personal or medical reasons) might be at a significant disadvantage relative to others without such concerns. Those in team sports or group efforts might particularly feel obliged to utilize them despite personal reservations, so as not to let their team down. Governing bodies will have to weigh whether they believe potential drawbacks such as these warrant restrictions on the usage of such interventions.

A blanket ban is unlikely to be fair in the event that reconsolidation-based memory modification becomes a common treatment for anxiety disorders. We have highlighted some hypothetical cases in which a sportsperson's level of anxiety seems quite trivial, but an athlete or other performer could be suffering from a truly disabling anxiety disorder. It would be highly unethical to prevent such a person receiving what could be the most effective treatment for their condition. If such individuals underwent a reconsolidation-based treatment, their post-treatment anxiety levels could end up below that of their peers, and it might then be seen as unfair to prohibit others from receiving such benefits.

Much more can be said about the use of "enhancers" in sports and other pursuits, and we welcome discussion of this issue. The use of memory-modifying procedures to target other normal but unpleasant experiences, such as an embarrassing faux pas, a difficult breakup, or grief, is also a possibility. Most people seem to accept these experiences for the normal events that they are, even though negative. We would argue that if people were willing to go through the troubles of a reconsolidation-based procedure, they would also be just as likely to seek non-pharmacological aids that are already available, such as low-intensity psychotherapy, counseling, or, even more simply, talking their problems over with close friends, meditation, and exercise. Nevertheless, there might be a risk that the availability of a seemingly easy and rapid intervention could reduce the willingness of people to go through the difficulties entailed in normal coping. A "quick-fix" society in which it is wrongly expected that any experience of discomfort can be rapidly removed without any effort would surely be anathema to all but the most committed hedonists. If the necessary drugs are readily available, it may be difficult to prevent people from attempting such uses, even if health care professionals restrict themselves to treating more severe psychological problems.

At a practical level, it is unclear whether reconsolidation-based memory modification would work to reduce relatively normal levels of fear or other emotions. The presence of only low-level anxiety may make sufficient memory reactivation or the triggering of reconsolidation itself very difficult in normal levels of fear or discomfort. Reconsolidation appears to function as an updating mechanism to ensure that learning aligns with reality (Lee 2009). It is likely to be more difficult to produce a situation in which the need for memory update is apparent for normal fears due to the lack of clear mismatch between what is expected and what occurs, relative to clearly overblown and irrational fears in which new learning can be expected even during a short exposure.

Attempts at reducing already quite low levels of fear might also tread on territory in which modifying the wrong memories becomes a nonnegligible risk. Where learned skills are involved, the memory for what must be performed itself should not be destabilized and made vulnerable to memory-modifying agents. Research suggests that motor skills can be rendered susceptible to disruption through a short reactivation followed by a novel motor-learning task (Walker, Brakefield, Hobson, and Stickgold 2003). It is unknown whether propranolol or other drugs represent a similar risk. This case may be analogous to declarative memory, in which interfering information is required for memory modification. Disruption may also be far more difficult with very-well-learned skills.

Such hypothetical issues represent clearly testable risk factors rather than insurmountable objections. However, dangers such as these would probably be increased if people try to self-administer treatments, as opposed to relying upon trained professionals with well-established procedures. Successful interventions require thoughtful design: Reductions in fear are not simply drug effects, but a combination of specific reactivation procedures and the administration of a memory-modifying agent within a restricted time window. Overblown media coverage may inspire confidence in a "magic pill" approach and encourage attempts at self-administration. Responsible and realistic reporting should therefore be promoted.

Despite potential drawbacks, some kinds of enhancement within the normal range might be clearly beneficial if successfully employed. As just one example, surgeons experiencing excessive performance anxiety before important or very intricate operations could have their anxiety permanently lowered in such situations, perhaps leading to improved performance (e.g., through reduced tremor) and better patient outcomes. Hence, the employment of reconsolidation-based memory modification techniques outside the typical realm of mental health might lead to further benefits as well as possible drawbacks.

MISUSES AND ABUSES

Even further outside of the traditional boundaries of mental health treatment than "enhancement" is the possibility of outright misuse and abuse. Conversations with peers and laypeople have made clear that military applications

of "anti-fear" interventions can be readily imagined. For example, a soldier could be exposed to a fearful combat situation or realistic simulation and then be given a memory-modifying drug that disrupts the reconsolidation of his or her fear. Alternatively, a reconsolidation-based manipulation might be used to try to disrupt a recruit's aversion to administering torture or other dubious tactics. However, the fact that such possibilities are readily imaginable does not mean they are readily achievable.

At a methodological level, both these applications pose complications. Current modifications of fear memories such as phobias or trauma deal with ego-dystonic, predominantly irrational, and maladaptive fears. Even after treatment, we observed a phobia participant respond fearfully when the tarantula bared its fangs in a legitimate threat display after clumsy handling. Hence, it seems that it is the irrational and hyperbolic fear that is tackled with these interventions. Combat situations are genuinely life-threatening, and a soldier's fear may be entirely justified and ego-syntonic. A certain degree of fear and stress is probably beneficial in combat, preventing reckless decisions and priming the body for action. Therefore, it may not even be desirable to interfere with these emotional responses for military purposes.

The reality of threat in war poses further problems for the unlikely prospect of generating a "super-soldier" with far less fear, because reconsolidation-based interventions do not simply dull the fear system. Experimental work from our lab has shown that even after reconsolidation-based disruption of learned fear, the very same fear can be easily relearned with experience (Soeter and Kindt 2011). This suggests that where legitimate threats are routinely encountered, corresponding emotional reactions will also be relearned. Hence, if a soldier with greatly reduced fear of combat were successfully produced, that soldier would not be immune to developing new fear responses as soon as he or she were exposed to the dangers of real-life battle again.

If a regime desired less fearful soldiers or especially ruthless interrogators, simple procedures are available to achieve this outcome. Personality testing, character assessments, and rigorous, transformational training have a long history in the military. Many instances of torture probably arise spontaneously, and where individuals are actively selected to take part in such acts, it is highly probable that this is based upon a proclivity toward or lack of aversion to such acts, as might be indexed by psychopathic traits in easily administered and well-validated tests (Hare and Vertommen 1991), or as simply made evident from behavior.

On the other hand, recruitment is often limited. This is particularly the case for less organized or more nefarious violent groups. It is conceivable that terrorist organizations might seek to ease the task of suicide bombers by reducing their fear.[4] As with military applications, such efforts would face a number of potentially insurmountable obstacles. Fear of death is not irrational, nor is a novel learning experience readily available; people only learn what awaits them on the other side of suicide once. Convincing people of the rewards they will reap in the afterlife, and the honor they will receive on earth, has proven sufficient without recourse to reconsolidation-based interventions. Furthermore, other means of inducing disinhibition, including alcoholic intoxication or hallucinogenic drugs, have a history of use in life-threatening situations from the ancient Aztecs up to modern warfare (Clendinnen 1991). Such intoxicants are easily accessible, easily used, and their effects already well known.

Finally, it is worth considering whether there might be military applications in which the line between use and misuse of such capabilities is not easily drawn. Most people are (rightly) concerned about the uses to which emotionless torturers or an army of fearless soldiers might be put, but if reconsolidation-based interventions could produce incremental improvements in the operations of an elite unit in a hostage situation or other crisis, such interventions may have more justification than at first appears.

Given the alternative means of selecting people for the job, the potentially adaptive nature of fear and stress in combat situations, and the difficulties in producing the desired results, it is unclear that anything would result from efforts to use reconsolidation-based interventions in the ways outlined in this section. Whether or not these possibilities can be realized, potential misuses of reconsolidation-based interventions should not deter those who aim to apply these methods for the relief of mental suffering. Most therapeutic instruments can be both a dangerous weapon and a tool of healing; we have the ability to prohibit certain uses while promoting others.

RECONSOLIDATION BEYOND ANXIETY

Reconsolidation research in humans has primarily focused on anxiety and trauma. However, the possibility of diminishing positive memories—either by accident or indirectly by interfering with trauma recovery and growth—has also been raised as an ethical concern. We have suggested that such effects are unlikely given appropriate care, but other types of positive memory may be at risk. Many theorists have likened romantic attachment to an addictive state (Burkett and Young 2012), suggesting that if a treatment could sever ties to an addictive substance (see later discussion), it might also be used to sever ties to a significant other. Given the lengths some people go to in order to move on from relationships, this is not too far-fetched a consideration. If used inappropriately, it might also be possible to diminish memories for positive events. We believe that doing so would likely require a purposeful effort, given the specificity of reconsolidation-based memory disruption we have observed. Nevertheless, some therapists or untrained individuals may misapply an otherwise highly useful technique. Hence, applications of

4. We thank Adam Kolber for raising this possibility.

reconsolidation-based treatments, and indeed any treatment, should be carefully scrutinized.

What has not been considered is the purposeful and therapeutic diminution of "positive" memories. The valence of a memory (positive or negative) is not indicative of its positive or negative impact on a person's life. Just as a strong aversive memory can prove highly adaptive (such as when it protects one against a genuine threat), the development of an overly potent appetitive memory can be hugely disruptive. This is evident in addiction, in which the rewarding properties of drug consumption have gained so much control over behavior that the drug is pursued even to the detriment of the person's health, relationships, and personal commitments (Hyman 2005; Milton and Everitt 2012).

Reconsolidation-based work has recently begun investigating whether appetitive memories are susceptible to post-reactivation disruption. Although strong demonstrations of reconsolidation-based memory modification in human studies have not yet been forthcoming, experimental work in animal models demonstrates that reconsolidation-based disruption of appetitive memories is a possibility (Lee, Di Ciano, Thomas, and Everitt 2005; Milton, Lee, and Everitt 2008). Further refinements to procedures, such as the means of reconsolidation disruption and the reactivation parameters, could produce a significant breakthrough in the near future. If the switch from addiction to sobriety could be made as rapid as that from phobic anxiety, then there could be repercussions beyond therapy, such as in the incarceration of individuals who committed crimes under the influence of, or to support, an addiction.[5]

Reconsolidation-based interventions for positive memories are not at this stage yet, and will never be a "magic pill" for mental disorders. One must also always consider systemic factors, such as the potentially pathogenic environment to which the treated individual returns. It is also possible that even a successful reconsolidation-based treatment will not induce such a rapid shift in the case of addiction. Nevertheless, such implications will only become more pressing as treatments progress, and might best be dealt with in advance. We invite discussion of other novel implications of rapid recovery from mental disorders, although we note that these would apply equally to any fast and effective treatment, not only reconsolidation-based ones.

CONCLUDING REMARKS

The remarkable malleability of memory allows for the development of treatments that can modify pathological memory traces. The therapeutic applications of the reconsolidation-based memory modification approach discussed in this article are just beginning to be realized, and disorders other than those discussed presently could be ameliorated using similar techniques. Alternative means of interfering with reconsolidation, including other pharmacological agents and purely behavioral procedures, may further expand the therapeutic potential of this field.

Undoubtedly, many of the issues raised could be discussed at further length, but we have aimed to show that fledgling concerns regarding the ethical implications of memory-modifying procedures have typically not taken account of actual experimental evidence and theoretical models, or can be challenged by research conducted since they were raised. If bioethical considerations are to be more than purely hypothetical concerns about yet-to-be realized developments, then it is imperative that they take contemporary research and theory into account. Conversely, researchers can be seen to be blind to the wider implications of their findings. We have highlighted a number of areas where there may be costs, as well as benefits, to research on memory reconsolidation. Interaction between those typically confined to ethics or research may help remedy the limitations inherent in any one perspective. ■

5. We thank Adam Kolber for highlighting this consideration.

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