Neurobiology of Learning and Memory 142 (2017) 108–117

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Review

Tackling maladaptive memories through reconsolidation: From neural to clinical science

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ARTICLE INFO

Article history:
Received 17 January 2017
Revised 7 March 2017
Accepted 8 March 2017
Available online 18 March 2017

Keywords:
Translational research
Memory reconsolidation
Anxiety disorders
PTSD
Clinical applications of reconsolidation
Prediction error

ABSTRACT

Behavioral neuroscience has greatly informed how we understand the formation, persistence, and plasticity of memory. Research has demonstrated that memory reactivation can induce a labile period, during which previously consolidated memories are sensitive to change, and in need of restabilization. This process is known as reconsolidation. Such findings have advanced not only our basic understanding of memory processes, but also hint at the prospect of harnessing these insights for the development of a new generation of treatments for disorders of emotional memory. However, even in simple experimental models, the conditions for inducing memory reconsolidation are complex: memory labilization appears to result from the interplay of learning history, reactivation, and also individual differences, posing difficulties for the translation of basic experimental research into effective clinical interventions. In this paper, we review a selection of influential animal and human research on memory reconsolidation to illustrate key insights these studies afford. We then consider how these findings can inform the development of new treatment approaches, with a particular focus on the transition of memory from reactivation, to reconsolidation, to new memory formation, as well as highlighting possible limitations of experimental models. If the challenges of translational research can be overcome, and if reconsolidation-based procedures become a viable treatment option, then they would be one of the first mental health treatments to be directly derived from basic neuroscience research. This would surely be a triumph for the scientific study of mind and brain.

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1. Introduction

The past century has seen radical shifts in the way we conceptualize and treat mental disorders. Dominant models of the mind and its maladies that have held sway at different periods have included psychoanalytic, behaviorist (which in its most radical form rejected the mind as an object of study), cognitive, and, more recently, neuroscientific perspectives. Within these broad delineations have been a plethora of variations on the major themes of each school of psychology, with corresponding treatment implications. While some treatments have been plainly ineffective or

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http://dx.doi.org/10.1016/j.nlm.2017.03.007
1074-7427/

even detrimental, controlled trials point to the efficacy of a host of different treatment approaches, but also significant room for improvement (Butler, Chapman, Forman, & Beck, 2006; Cuijpers et al., 2013; Leichsenring, 2001; Shedler, 2010). Even in cognitive behavioral therapy (CBT), currently the most widely recognized evidence-based treatment, research suggests that a substantial portion of patients may fail to achieve significant improvements, and a large proportion of successfully treated patients go on to relapse (Durham, Higgins, Chambers, Swan, & Dow, 2012; Hofmann & Smits, 2008; Loerinc et al., 2015).

In light of the imperfection of current treatments and the ever expanding arsenal of different approaches, several authors who stand at the interface of research and practice have called for a move away from the relatively simple question of which of the many therapeutic approaches work to an understanding of why (Kazdin, 2001; McNally, 2007).[1] If reached, a clear understanding of the underpinnings of mental disorder and mechanisms of change could transform research in mental health treatment from a more descriptive science – cataloguing what works – to an explanatory one – explaining why such treatments are effective – or even a predictive one, proposing what will work best in novel situations given an understanding of the root problems and the means through which they can be tackled. Interdisciplinary dialogue, and particularly the translation of findings from different levels of analysis, will prove essential in this endeavour. At present, only basic and behavioral neuroscience research (by which we mean *in vitro* and *in vivo* animal models, rather than functional imaging in humans) can deconstruct the low level neural networks that underpin mental disorders, but only in combination with human experiments and clinical trials can the relevance of this basic knowledge be assessed and its value for clinical practice realised. Current work in models of exposure therapy highlights the potential utility of such a translational approach.

Exposure is a technique commonly used in the treatment of anxiety disorders, in which patients are confronted with their fears. This may be *in vivo* (i.e. confrontation with external stressors in real-life), imaginal (i.e. exposure to feared situations or memories through the imagination), interoceptive (i.e. exposure to feared internal sensations), or, more recently, in virtual reality (i.e. using virtual reality technology to construct analogues of real-world situations) (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) 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. Yet, more 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, inhibitory memory trace that competes with original learning for control over behavior (Bouton, 2002). Changes in context, aversive events, or the simple passage of time can lead to the resurgence of the old memory. 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.

As Craske and colleagues have emphasized, if exposure therapy operates through the formation of an inhibitory memory trace, then clinicians should aim to optimize this inhibitory learning (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014; Craske et al., 2008). For example, rather than simply 'habituating' patients to a feared stimulus (exposing them until their fear levels drop), treatments ought to focus on violating the patient's expectations about negative outcomes that might occur upon exposure to the feared stimulus, as large prediction errors are thought to generate strong inhibitory memories. Insights into treatment mechanisms also have somewhat counterintuitive implications. Rodent and human experimental research indicates that providing occasional reinforcement (negative outcomes) during extinction might actually reduce spontaneous recovery (Bouton, Woods, & Pineño, 2004; Gershman, Jones, Norman, Monfils, & Niv, 2013; Woods & Bouton, 2007). Occasional reinforcement or gradual extinction may reduce the disparity between new learning and the original memory, potentially acting directly on the original memory or meaning that later negative outcomes don't automatically activate the maladaptive memory trace because the new, more adaptive one also contains (and can therefore be more easily activated by) aversive experiences. Again, conceiving of change through the lens of inhibitory learning and competing memory traces could serve to enhance treatment outcomes.

In summary, understanding mechanisms of change in treatment, and the underpinnings of the disorders we wish to treat, are crucial goals for mental health research if the aim of this is to optimize available as well as novel treatments. However, in the push to realise the potential of treatment approaches, lessons learned from lower levels of analysis (which are not always easily translatable to the clinic and frequently impose limitations on the scope of applications) are not necessarily taken on board. Research pushing the boundaries of our current knowledge through the attempted translation of lab work into therapeutic approaches is necessary for the advancement of any novel treatment approach, but efforts in this direction must be informed by the most relevant available research.

In this paper, we focus on attempts at disrupting reconsolidation of maladaptive memories in anxiety and trauma-related disorders through pharmacological means, and particularly the use of propranolol in humans. Many of the issues we highlight, however, would most likely apply to other approaches inspired by the idea of reconsolidation, such as performing extinction after a brief reminder cue (Monfils, Cowansage, Klann, & LeDoux, 2009), or to the use of other pharmacological agents aiming to block reconsolidation, and the overarching message that clinical interventions should aim to understand mechanisms of change and take account of the most relevant research is of course applicable to all mental health treatments. It is also conceivable that reconsolidation might be harnessed so as to enhance certain adaptive memories, though this will not be explored in the present review. In the following sections, we briefly outline current research into the pharmacological disruption of memory reconsolidation and attempts to translate this into clinical interventions. Then, we draw upon insights from experimental research on reconsolidation in humans and animals to make some empirically grounded suggestions for reconsolidation-based treatments. We also consider limitations of current experimental models, and suggest several avenues that can be pursued in future research.

2. Memory reconsolidation

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 changes (Kandel, Dudai, & Mayford, 2014, though see discussion of this below). Protein synthesis inhibitors (PSIs) prevent the expression of long-term

[1] The term 'relatively' is sincerely meant: designing studies that do justice to the different therapeutic approaches under investigation, in a controlled yet clinically relevant setting from which meaningful conclusions can be drawn, is of course very difficult.