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Intervention strength does not differentially affect memory reconsolidation of strong memories

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ABSTRACT

Recently, it has become clear that retrieval (i.e., reactivation) of consolidated memories may return these memories into a labile state before they are restored into long-term memory ('reconsolidation'). Using behavioral manipulations, reactivated memories can be disrupted via the mechanism of novel learning. In the present study, we investigated whether changing a strong memory during reconsolidation depends on the strength of novel learning. To test this, participants ($N = 144$) in six groups acquired a relatively strong memory on Day 1 by viewing and recalling a series of pictures three times. On Day 8, these pictures were reactivated in three groups, and they were not reactivated in the other three groups. Then, participants viewed and recalled new pictures once (weak new learning) or three times (strong new learning), or they did not learn any new pictures. On Day 9, participants performed a recognition test in which their memory for Day 1 pictures was assessed. Two main results are noted. First, the groups that reactivated pictures from Day 1 and received weak or strong new learning did not differ in memory performance. Second, these two groups consistently performed similar to groups that controlled for new learning without reactivation. Because these results contradict what was expected based on the reconsolidation hypothesis, we discuss possible explanations and implications.

1. Introduction

More than a century ago, Müller and Pilzecker (1900) proposed the memory consolidation hypothesis. It stated that memories of newly learned information are initially in a dynamic, labile state before they become fixed in long-term memory ('consolidation'), and that once they are consolidated, they are resistant and insensitive to interference by distracting stimuli, injuries, or toxins (see McGaugh, 2000; see Dudai, 2004; though see, Loftus & Palmer, 1974). Recently, however, it has become clear that retrieval (i.e., reactivation) of consolidated memories may return these memories into a labile state before they are re-stabilized ('reconso lidation') (Nader, Schafe, & LeDoux, 2000). During reconsolidation, the memory trace can be strengthened, weakened, or updated (for an overview see Besnard, Caboche, & Laroche, 2012; Schwabe, Nader, & Pruessner, 2014; Ågren, 2014).

Disruption of memory during the reconsolidation process was first observed in animals that received amnesic agents (i.e., anisomycin) shortly after memory reactivation of conditioned threat memories (e.g., Dębiec, LeDoux, & Nader, 2002; Nader et al., 2000). These agents blocked protein-synthesis, which is necessary for long-term memory formation, and caused amnesia for the original threat memory. Research on human reconsolidation quickly followed and primarily targeted conditioned threat memories with pharmacological manipulations that were safe for humans such as propranolol (e.g., Brunet et al., 2008; Kindt, Soeter, & Vervliet, 2009; Sevenster, Beckers, & Kindt, 2012, 2013, 2014; Soeter & Kindt, 2012). However, recent studies – including a meta-analysis – have shown that the effects of pharmacological interventions on human reconsolidation are not consistent (Lonergan, Olivera-Figueroa, Pitman, & Brunet, 2013; Wood et al., 2015).

An alternative approach to disrupting memories during the reconsolidation process is by use of behavioral manipulations (Forcato et al., 2007; Hupbach, Gomez, Hardt, & Nadel, 2007; Hupbach, Gomez, & Nadel, 2009; Hupbach, Hardt, Gomez, & Nadel, 2008; James et al., 2015; Kredlow & Otto, 2015; Schiller et al., 2010; Schwabe & Wolf, 2009; Wichert, Wolf, & Schwabe, 2011, 2013a, 2013b). Behavioral manipulations that change memories during reconsolidation typically focus on the mechanism of memory updating or interference after reactivation, and usually follow a three-day design that mirrors research with amnesic agents. On Day 1 encoding of a novel memory takes place. On

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Day 2, participants in the experimental group reactivate the memory, and then encode new, yet comparable memories. Typically, there are also conditions that only reactivate the memory, only receive the manipulation, or do not get tested on this day (i.e., control conditions). On the third day, there is a test of memory strength of the original encoded material. Overall, these studies have shown that new learning after reactivation on Day 2 yields effects on Day 3. They found deteriorated recall of the original encoded material, which was interpreted as updating of the original memory by incorporating the newly encoded information (e.g., Schwabe et al., 2014).

Several boundary conditions have been identified which preclude memories from being disrupted during reconsolidation (e.g., Schwabe et al., 2014). For instance, older and stronger memories are more resistant to post-reactivation modification compared to younger and weaker memories (Eisenberg, Kobilo, Berman, & Dudai, 2003; Wichert et al., 2011). Some studies show that these boundary conditions can be overcome and that post-reactivation modification during reconsolidation can still take place (e.g., Wang, de Oliveira Alvares, & Nader, 2009; Winters, Tucci, & DaCosta-Furtado, 2009). For instance, Wichert et al. (2013a) showed that, compared to weak episodic memories, strong episodic memories (i.e., memories that were repeatedly reactivated without subsequent new learning) are more resistant to the effect of new learning during reconsolidation. The effects of new learning interventions resulted primarily in loss of the original memory for those memories that were weak. This happened to a smaller extent for memories that were strong. There were no signs of updating (i.e., incorporation of new information into the original memory) for either weak or strong memories. Overall, this shows that strong memories are still sensitive to modification during reconsolidation, but to a lesser extent than weak memories.

It is likely that the extent to which memories can be changed is not solely dependent on the strength of the initial memory, but also on the strength of the post-reactivation manipulation. In animal research, the impact of the post-reactivation manipulation is dose-dependent: increasing the dose of the amnesic agent increases memory impairment (Duvarci, Nader, & LeDoux, 2008; Nader et al., 2000). Recently, Wichert et al. (2013b) investigated the effect of different doses of behavioral post-reactivation manipulations on the memory reconsolidation process in humans. On Day 1 in their experiment, participants (in six groups) acquired a relatively weak memory by viewing and recalling a series of pictures once. One week later (Day 8), these pictures were reactivated in three groups, and they were not reactivated in the other three groups. Then, of these three groups, one group learned new pictures once (weak manipulation), another learned new pictures three times (strong manipulation), and another did not learn new pictures. Hence, the number of exposures to new materials primarily determined the intervention's strength. Two weeks after the testing first day (Day 15), participants performed a recognition test in which they saw the original pictures from Day 1, the newly learned pictures from Day 8, and a completely novel set of pictures. These pictures were intermixed and for each picture participants were asked to classify whether they had seen it on Day 1 by pressing a yes or no button. In line with findings from pharmacological manipulations, Wichert et al. showed that, following reactivation, learning new pictures once had no effect on episodic memory while learning these pictures three times did. That is, the reactivation + strong manipulation group showed memory change compared to all other groups. This change reflects incorporation of new information into the original memory, but no loss of the original memory. This shows that the extent of modification of a relatively weak memory is affected by the strength of new learning after reactivation. However, it is currently unclear how post-reactivation manipulations affect *strong* memories.

Knowledge about how to change strongly encoded memories can have important implications for the behavioral treatment of psychiatric disorders where dysfunctional memories are a core feature (Dębiec, 2012; Parsons & Ressler, 2013; Schwabe et al., 2014). For instance, core symptoms of post-traumatic stress disorder are intrusive memories of a traumatic event, which are memories that are overconsolidated due to the release of stress hormones in reaction to the traumatic event (Pitman, 1989), and the intrusive and repetitive nature of the traumatic memory (Hackmann, Ehlers, Speckens, & Clark, 2004). Using behavioral interventions during reconsolidation in clinical practice could entail that patients recall (i.e., reactivate) their memory and receive an appropriate intervention that modifies the memory (Beckers & Kindt, 2017; Lane, Nadel, Greenberg, & Ryan, 2015). Given this potential clinical application, an important question is how strong memories can be changed during reconsolidation by post-reactivation behavioral manipulations that differ in number of exposures.

In the present study, we investigated whether reconsolidation of *strong* memories is dependent on the strength of the post-reactivation manipulation. To test this, we used the three-day paradigm developed by Wichert et al. (2013b), but made three modifications: the strength of the initial memory on Day 1, the time between the final two days, and we added the remember/know distinction. Therefore, in our study on Day 1, participants in all six groups acquired a relatively strong memory by viewing and recalling a series of pictures three times (instead of once). On Day 8 – one week later –, these pictures were reactivated in three groups, and they were not reactivated in the other three groups. Then, participants viewed and recalled new pictures once (weak novel learning) or three times (strong novel learning), or they did not learn any new pictures. On day 9, which was one day instead of one week later, participants performed a recognition test in which they saw the picture sets from day 1 and day 8, and a novel picture set. For each picture, they decided whether they had seen it on day 1 by pressing a yes or no button, and whether they associated it with a feeling of remembering or knowing. The shortened time interval of 24 h between intervention and test was based on Wichert et al. (2013a). Theoretically, the duration of this interval is largely irrelevant as long as the test on the final day is placed outside the reconsolidation window (approximately 4–6 h after reactivation), which is the case in the current study. Moreover, with a shortened interval reconsolidated memories are less prone to general memory decay. Given that strong memories remain sensitive to modification during reconsolidation (see earlier pharmacological studies) and that post-reactivation manipulations are dose-dependent, we expected that strongly consolidated memories would be altered more by applying the strong post-reactivation manipulation after reactivation than by the weak manipulation.

2. Method

2.1. Participants and design

Students from Utrecht University and the University of Applied Sciences ($N = 144$, 72 men, 72 women; $M_{age} = 21.14$ years, $SD = 2.27$) participated for course credit or a monetary compensation. Participants were excluded if they reported a current or chronic mental disorder, drug abuse, current treatment with medication, or if they were younger than 18 or older than 30 years. All participants provided written informed consent. The Ethical Committee of the Faculty of Social and Behavioral Sciences at Utrecht University (FETC15-001) approved this study.

Participants were assigned to one of six groups using block randomization. Groups were constituted by whether there was