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Review

Human reconsolidation: A reactivation and update

Thomas Agren*

Department of Psychology, Uppsala University, Uppsala, Sweden

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ABSTRACT

The reconsolidation hypothesis states that memories, when reactivated, enter a transient, labile state followed by a re-stabilization termed reconsolidation. By affecting the reconsolidation process, memory persistence can be influenced, leading to memory enhancement or decrement. This is a time-dependent process and the result of modulating reconsolidation is present only after the reconsolidation process is completed. Historically, reconsolidation research has been performed on non-human animals, since the methods originally used for reconsolidation disruption are not safe. However, there now exist several techniques safe for humans, and consequently, in recent years, papers on human reconsolidation have emerged. Here, the existing literature on human reconsolidation is reviewed and discussed, including studies on fear memories, appetitive memories, procedural memories, and declarative memories. Methods of memory reactivation are compared between studies, and the consistency and lack of consistency in results over reactivation methods and memory types are discussed. These results provide future challenges, both experimental and clinical, in defining the boundary conditions and mechanisms governing the reconsolidation phenomenon.

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* Correspondence to: Department of Psychology, Uppsala University, Box 1225, SE-751 42 Uppsala, Sweden. Tel.: +46 18 4712124; fax: +46 18 4712400.
E-mail address: thomas.agren@psyk.uu.se

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1. Introduction

A newly formed memory becomes a stable memory trace through a consolidation process that follows encoding. The process of consolidation is dependent on protein synthesis and is modulated by components of a stress reaction, such as noradrenaline and glucocorticoids, in a process in which the amygdala is vital (McGaugh, 2000). However, a consolidated memory is not set forever. Recalled or reactivated memories can under certain circumstances enter a transient labile phase followed by a new stabilization process termed reconsolidation. Thus, reconsolidation seems to be a time-dependent process and the effects of reconsolidation modulation should be observable after concluded reconsolidation, and not immediately upon administration. Reconsolidation is a phenomenon found in a range of species and types of memory, making it appear as an often employed memory strategy in nature (Alberini, 2005). During reconsolidation, memories can be enhanced (Rodriguez et al., 1999), impaired (Nader et al., 2000), or updated with new information (Lee, 2008). The term 'reconsolidation' is perhaps unfortunate; since the reconsolidation process appears to be something else than a simple repeat of the consolidation that follows directly on encoding. The differences and similarities in the molecular mechanisms of consolidation and reconsolidation are comprehensively discussed elsewhere (Alberini, 2005; Tronson and Taylor, 2007). However, the term 'reconsolidation' has firmly established itself within the scientific community and is unlikely to be replaced.

Studies on reconsolidation have mostly been performed on animals. The first methods used to disrupt reconsolidation were electroconvulsive shocks (Misanin et al., 1968) and the administration of protein synthesis inhibitors (Nader et al., 2000). The first study to experimentally examine the reconsolidation process in humans used electroconvulsive shocks for reconsolidation disruption. Participants encoded a set of pictures of items and a set of word pairs which were tested with recognition memory tests. On these tests, it seemed that consolidation could be disrupted by electric shocks, but no effect of electroconvulsive shocks on reconsolidation was found. The study also tested the subject's memories of TV shows, watched years before the study. These older memories were not affected by the shocks at all (Squire et al., 1976). Also, early clinical trials used electroconvulsive therapy (ECT) and disrupted the reconsolidation in patients with OCD and hallucinations with some success (Rubin, 1976). Still, ECT is deemed too risky for general experimental use and protein synthesis inhibitors are also not safe for humans. However, memory enhancement and erasure by affecting reconsolidation have recently been shown, by use of pharmacological manipulations that are safe for humans (Brunet et al., 2008; Kindt et al., 2009), and behavioural means (Schiller et al., 2010; Walker et al., 2003). Consequently, the last few years have produced quite a few studies on human reconsolidation and the present paper aims at summarizing what we have learned.

Reconsolidation processes are typically studied with a three-day experimental design (Fig. 1). On the first experimental day, encoding takes place. On experimental day 2, the memory is reactivated, and manipulated. Usually, there is a control group that does not receive the manipulation, or receive the manipulation after a delay, when the reconsolidation process is supposed to be concluded. There is also typically a control group that do not receive a reactivation, showing that the effect of manipulation is dependent on a memory reactivation. Finally, on experimental day 3, there is a test of memory strength. Sometimes, there are further follow up tests. In clinical studies, the patients are viewed as already possessing the memories, and instead of experimental day 1, baseline measures are obtained, and then the subjects proceed directly to experimental day 2.

1.1. Methods of reconsolidation manipulation

The results below will be structured according to method of reconsolidation manipulation and type of memory. Listed below are the methods used for reconsolidation manipulation in humans, along with the rationale on why these methods are used, drawing on the literature on rodent consolidation, rodent reconsolidation, and human consolidation.

1.1.1. Propranolol

The most frequently used pharmacological manipulation is the administration of the drug propranolol, a β-adrenergic antagonist. Its presumed function on memory is through adrenergic β receptors coupled with the adenylyl cyclase-linked G-protein receptors governing the cAMP cascade that leads to protein synthesis-dependent long-term memory formation (Przybyslawski et al.,

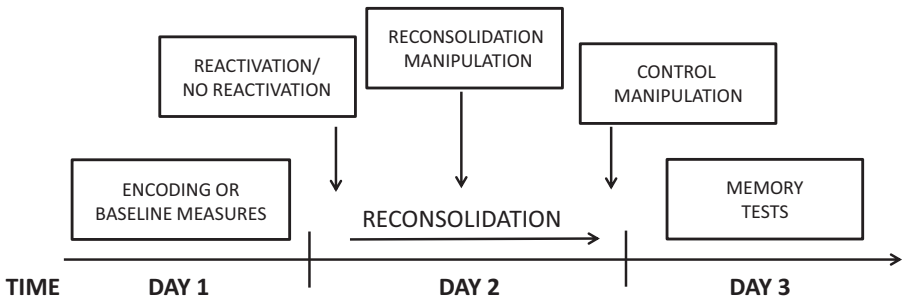

Fig. 1. Typical three-day experimental design for the study of human reconsolidation. On day 1, subjects participate in an encoding session. On day 2, the memory is reactivated, triggering a reconsolidation process. A control group, in which the memory is not reactivated, is often included. The on-going reconsolidation process is then manipulated. An additional control group does not receive this manipulation, or receives a control manipulation after the reconsolidation process is concluded. Finally, on day 3, the memory is tested. In clinical trials, the encoding of day 1 is replaced by baseline measurements of the traumatic memory to be treated.

1999). Beta-adrenergic activity in the amygdala was first tied to memory processes in the late 1970s when post-training injections of propranolol in rodents produced decreases in retention of an inhibitory avoidance task. Specifically, propranolol produced decreases in retention when injected shortly after training, but not when injected 6 h after training, indicating that a limited period of consolidation could be targeted (Gallagher et al., 1977). Later reports have shown that systemic propranolol injections, also when injected shortly after the reactivation of a memory, decreases the retention of both an inhibitory avoidance task (Przybyslawski et al., 1999) and fear conditioning (Debiec and Ledoux, 2004) in rodents, demonstrating that propranolol effectively modulated memories also during a limited period of reconsolidation. Both studies suggested propranolol as a possible treatment for the weakening of traumatic memories in patients with post-traumatic stress disorder (PTSD). In line with this, an important study in humans noted that propranolol disrupted the consolidation of emotional, but not neutral memories, showing that the strengthening of memories through modulation of stress reaction components (Cahill and McGaugh, 1995; McGaugh, 2004) could be blocked by a β-adrenergic antagonist (Cahill et al., 1994). These results spawned research of propranolol use on reconsolidation of human fear memories.

1.1.2. Stress/cortisol

Components of the stress reaction have consistently been found to affect the consolidation of memories (Cahill et al., 1994; McGaugh, 2004, 2000) and studies in rodents have reported that reconsolidation processes are also affected by stress (Cai et al., 2006; Wang et al., 2008). A stress reaction has many components including: (1) the activation of monoaminergic systems leading to release of noradrenalin, acetylcholine, serotonin and dopamine throughout the brain, (2) the release of glucocorticoids, and (3) activation of the sympathetic nervous system leading to elevation of heart rate and blood pressure (Rodrigues et al., 2009). However, studies that are concentrating on evaluating the stress reaction in humans generally do a manipulation check by measuring cortisol. That, and the fact that the results from studies using propranolol and stress administration seem to fall into two different categories, is the reason for their separate classifications in this review. Specifically, when stress is used to modulate reconsolidation, an immediate effect on memory is often reported, that is, before reconsolidation has concluded.

1.1.3. Behavioural means

In the study of declarative memories, there is a long tradition of research on interference, that is, how additional learning, following initial learning, can disrupt the original memory. This phenomenon has previously been studied in the framework of consolidation, and is now also studied in the framework of reconsolidation (Robertson, 2013). Regarding fear memories, Monfils et al. (2009) demonstrated that reconsolidation of a conditioned fear memory could be disrupted by behavioural means, namely by extinction. Extinction is a process by which conditioned fear is diminished by repeated presentations of the conditioned stimulus without presentation of the fearful stimulus. In a series of experiments, extinction was shown to disrupt the reconsolidation of fear memories in rodents, showing less remaining fear in tests of spontaneous recovery, renewal, and reinstatement (Monfils et al., 2009). This result was translated to humans in 2010 (Schiller et al., 2010) and has since been followed by several studies.

1.1.4. Glucose

Glucose is a naturally occurring motivational factor for nutrition. It is important for an organism to remember where food is available, and hence, to enhance associated memories. In line with this, glucose (and fructose) have been found to enhance memory both in rodents and humans (Messier, 2004) and also to affect memory reconsolidation (Rodriguez et al., 1999). The mechanisms through which glucose interacts with memory is unknown, but two alternatives are, insulin-receptors in the hippocampus (Stern and Alberini, 2013), or through the interaction of circulating glucose with one or several neurotransmitter systems – see Rodriguez et al. (1999) for a discussion.

1.1.5. Ketamine

There is a vast literature on the impact of glutamate receptor activity on learning and memory (Riedel et al., 2003). Ketamine is an antagonist of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor and has successfully been used to affect consolidation (Parwani et al., 2005; Wang et al., 2006) and reconsolidation (Zhai et al., 2008). The memory mechanisms using glutamate receptor activity is a far too extensive subject to be included in this review, for a discussion, see Riedel et al. (2003).

2. Memory subtypes

Memories are in this review partitioned into the following types: (1) fear memories, or memories created by aversive reinforcement and of clinical interest for the treatment of anxiety, (2) appetitive memories, or memories created by rewarding reinforcement and of clinical interest for the treatment of drug abuse, (3) procedural memories, or memories of motor skills, and (4) declarative memories, or memories participants recall using a conscious effort. There are some memories with emotional content in the last category which somewhat blurs the line between declarative and fear memories.

2.1. Fear memories

The possibility of attenuating the strength of fear memories by disrupting their reconsolidation has yielded a lot of interest in recent years. This is because there could be important clinical implications for the treatment of anxiety disorders dependent on fearful and traumatic memories, in particular PTSD, but also specific phobia. The non-clinical experimental studies on fear memories all involve fear conditioning. Fear conditioning is a process by which repeated paired presentations of a neutral stimulus and an aversive stimulus creates an association between the neutral and aversive stimuli such that the neutral stimulus also becomes aversive and able to produce a fear reaction by itself. In short, a fear memory in these studies consists of a learned association between a neutral and an aversive stimulus. Anxiety disorders have long been considered as reflecting possible deficits in the processes governing fear conditioning. Indeed, Pavlov himself proposed that the development of anxiety occurred by the means of fear conditioning (Pavlov, 1927). Exposure therapy, a treatment based on the process of extinction, is highly effective in treating anxiety disorders. Moreover, phenomena that follow extinction in fear conditioning are also found in clinical populations after treatment with exposure therapy (Mineka et al., 1999; Rachman, 1989). Hence, there is reason to believe that experiments with fear conditioning may provide insights useful in a clinical setting. The clinical studies on fear memories are so far concentrated to PTSD, but there is also great interest in the possibility for trials with specific phobia.

2.1.1. Propranolol

In 2008, Brunet et al. published the first clinical study using propranolol for reconsolidation disruption of traumatic memories in PTSD patients. Subjects reactivated their traumatic memories by describing them, after which one group ($n = 9$) received propranolol and the other group ($n = 10$) placebo pills. After a week, patients

listened to the script created from their descriptions. During both the initial reactivation and the follow-up test, psychophysiological measures were taken. For a first clinical study, it showed promising results with the propranolol group exhibiting significantly lower heart rate and skin conductance during the follow-up test. However, because a control group which received propranolol without the memory reactivation was not included, the results could be a product of non-memory specific influence of the drug (Brunet et al., 2008). Since then, a few clinical trials in three different countries (Canada, USA, and France) have reported improvements in patients with PTSD (Brunet et al., 2011, Poundja et al., 2012). Again, in these clinical trials there were no control groups receiving placebo or propranolol treatment without reactivations.

The experimental studies that have used propranolol for disruption of reconsolidation of fear memories have included control groups. Using a typical three-day experiment, Kindt et al. (2009) used propranolol administration for manipulating the reconsolidation process. A session of extinction and a reinstatement memory test on day 3 showed that the combination of propranolol administration and memory reactivation in the form of reminder retrieval, led to diminished fear expression as well as absence of the expected return of fear usually noted after reinstatement of conditioned fear. On the other hand, the combination of propranolol and no memory activation, as well as the combination of placebo pill and memory activation, produced a return of potentiated fear startle as expected using reinstatement on conditioned fear. No difference in declarative memory was found between groups. Propranolol was administered 90 min before the reactivation in order to perform the reactivation at peak plasma concentration. This leaves a possibility that the drug may have affected the memory during the reactivation and not necessarily through reconsolidation, although which memory mechanism would be used to affect the memory in such a way is unknown. However, this result has since been replicated with propranolol administered after the reactivation (Soeter and Kindt, 2012a).

A replication of the study, also using propranolol as manipulation of the reconsolidation process, showed similar results, with the addition that the attenuation of fear persisted also a month after the original fear learning (Soeter and Kindt, 2010). In another study, propranolol was found to stimulus-specifically attenuate the spontaneous recovery, reinstatement, and reacquisition of startle reactions. Moreover, the study found a possible generalization of the effect to other pictures in the same fear-relevant category, that is, if a spider picture was reactivated and reconsolidation was disrupted, the reduced fear at later tests generalized to another picture of a spider (Soeter and Kindt, 2011). What makes this result remarkable is that the generalization test was done after a reacquisition procedure. The authors propose that the reconsolidation blockade not only neutralizes the original memory trace, but also suppresses synaptic plasticity. To strengthen this argument, they present results from an additional experiment where acquisition, using the same experimental design as the reacquisition in the original experiment, was enough to induce fear generalization such that acquisition to a stimulus increased the fear reaction to a picture of the same category. Thus, the authors argue that such fear generalization would have taken place in their original experiment if it was not for the reconsolidation blockade. In other words, in spite of the strengthening of the fear reaction during the reacquisition, given a short break (according to the paper, about the same time period as between stimuli in reacquisition), the reaction to a stimulus in the same category hinged on the state of the memory trace of the original stimulus after the reconsolidation on the previous day.

As previously noted, components of a stress reaction, such as noradrenalin and cortisol, strengthen the consolidation of memories. If reconsolidation disruption is to be a viable alternative for treatment of traumatic memories, the effect must be shown also for these resilient memories. In an attempt to create such memories experimentally, Soeter and Kind administered yohimbine, an α2-adrenergic receptor antagonist known to stimulate central noradrenergic activity, before fear acquisition (Soeter and Kindt, 2012a). Two stimuli were conditioned to a shock, but only one reactivated on day 2. The administration of the yohimbine did not block the reconsolidation effect, since the fear reactions to the reactivated stimulus was still diminished by propranolol. Interestingly, the stimulus that was not reactivated, and hence, did not get its reconsolidation disrupted by propranolol, showed a slower extinction if yohimbine had been administered day 1, as compared to placebo.

Furthermore, propranolol has been found to disrupt an instructed fear memory. Participants were instructed that one of two fear-relevant stimuli would be followed by a very unpleasant electric shock, while the other stimulus would not. This yielded a potentiated startle response to the stimulus associated with a shock, although no shock was ever administered. Twenty-four hours later participants received propranolol or placebo and were again instructed that the picture could be followed by a shock, and that the risk would be higher if you did not receive a shock on the previous day. They were then exposed to a presentation of the stimulus. Day 3, both fear reactions and subjective distress during extinction and renewal were diminished for the propranolol group (Soeter and Kindt, 2012b).

In order to examine the elements needed to induce a labilization of memory to initiate a reconsolidation process, Sevenster et al. (2012) used the design from Kindt et al. (2009), but had one group receive the day 2 reactivation without the shock electrodes attached. This, they argued, presented a situation in which the association between stimulus and shock had no reason to be updated, because no new information about the association could be learned. Although shock electrodes were not attached, subjects had elevated startle response at reactivation, but the subsequent administration of propranolol did not remove the fear reactions on day 3 (Sevenster et al., 2012). These results were followed with a clever study that manipulated the expectancies of the participants by varying the acquisition reinforcement rate between groups. Two groups received fully reinforced differential conditioning and were, in addition, instructed of the contingency. On day 2, these groups were shown a reinforced, or an unreinforced stimulus respectively. A third group had acquisition partially reinforced and was shown a reinforced stimulus on day 2. All groups also received propranolol on day 2. On day 3, memory strength was tested with extinction and reinstatement. The fully reinforced group naturally expected a shock to be associated with stimulus also on day 2. Thus, they made a prediction error when they were shown the stimulus without shock. On day 3, their memory strength was markedly decreased by propranolol. The other fully reinforced group, which instead was shown a reinforced stimulus on day 2, and thus did not make a prediction error, did not seem to have their memory affected by the propranolol. When the partially reinforced group was shown a reinforced stimulus on day 2, their expectancies of shock increased, indicating that also they made a prediction error. This group also had their memory decreased by the propranolol (Sevenster et al., 2013). Thus, it would appear that prediction error is vital for a reactivation of memory to trigger a reconsolidation process. This supports the notion that a function of reconsolidation is memory updating.

In the above studies, an effect of reconsolidation was found using startle potentiation, but not skin conductance responses. This suggests that there may be multiple memory systems working in parallel, where some boundaries for reconsolidation are found for a memory governing a certain type of fear reaction, but not for another. The authors of these studies argue that this is because electrodermal responses are supposedly more associated

with declarative knowledge (conscious awareness of the contingencies of the fear learning and extinction) and predominantly hippocampal-dependent, in contrast to startle, that is not dependent on declarative knowledge and predominantly amygdala-dependent. This may be the case, but it is somewhat controversial to claim that skin conductance is dependent upon hippocampus and declarative memories. Firstly, humans can be fear conditioned, as measured with skin conductance responses, without contingency awareness, and thus, without declarative memory (Ohman and Soares, 1993; Schultz and Helmstetter, 2010). Also, the amygdala has been shown to be necessary for fear conditioning in humans using skin conductance measures (Bechara et al., 1995) and several studies show a correlation between amygdala activity and skin conductance (Furmark et al., 1997; LaBar et al., 1998). Still, it appears further studies are needed in order to understand the differences in results between the startle and skin conductance results.

2.1.2. Ketamine

Corlett et al. (2013) used ketamine to modulate the reconsolidation of fear memories. On day 1, participants were conditioned, using an auditory stimulus as UCS. On day 2, participants received either placebo or ketamine after the memory reactivation. On day 3, memory was tested with a re-extinction and reinstatement. Participants showed an increased responding, as measured with skin conductance, to the cue reactivated in conjunction with ketamine, as compared to placebo, in both re-extinction and reinstatement. This result is somewhat surprising, since ketamine has known amnesic effects, which the authors also point out. Interestingly, the subjects who reported the most distorted perceptual experiences showed the most ketamine-induced fear increase (Corlett et al., 2013).

2.1.3. Behavioural means (extinction)

Schiller et al. (2010) was first to translate the reactivation–extinction paradigm to humans. In their study, using the typical three-day design, subjects underwent fear conditioning to induce an experimental fear memory on day 1. Twenty-four hours after the initial training, they received a fear memory reminder consisting of a presentation of the conditioned stimulus. One group of subjects then received extinction training 10 min later, hence during the reconsolidation interval, and one group received extinction training 6 h later, after reconsolidation was supposedly completed. Spontaneous recovery was tested another 24 h later using a second session of extinction. Return of fear, as measured by skin conductance responses, was noted in the group that received extinction training outside of the reconsolidation interval and hence, after completed reconsolidation, while no return of fear was noted in the group which received reconsolidation disruption, that is, extinction training during the reconsolidation interval. A control group, which received no memory reactivation before extinction, also showed a return of fear. Remarkably, at a follow-up test one year later, the effect seemed to linger. Moreover, in a second experiment, two stimuli were conditioned day 1, but day 2, only one was reactivated before an extinction session diminished the fear reaction to both stimuli. During the reinstatement memory test day 3, the stimulus that was reactivated before extinction showed significantly less return of fear than the non-reactivated stimulus. Thus, showing a specific effect of extinction on reconsolidation dependent on the memory reactivation (Schiller et al., 2010).

However, attempts at replicating these results have yielded mixed outcomes. Kindt and Soeter (2011) conditioned participants to two fear-relevant stimuli on day 1. On day 2, only one of the two stimuli was reactivated before both were extinguished. On day 3, spontaneous recovery was tested with re-extinction and reacquisition after a reinstatement procedure. The study measured fear potentiated startle, skin conductance responses, and expectancies, continuously during the experiment, but found no effect of disrupted reconsolidation on the reactivated stimulus. Instead, a return of fear was found to both stimulus, observed with all measures (Kindt and Soeter, 2011). The authors considered if somehow the fear-relevant stimuli may have rendered the process ineffective. However, a later study used both fear-relevant and fear-irrelevant stimuli with the same experimental design, and also found no effect of reconsolidation disruption (Golkar et al., 2012). Oyarzún et al. (2012) did find an effect of reconsolidation disruption as measured with skin conductance responses. They used a three-day design with reinstatement and re-extinction as memory probes day 3. Instead of an electric shock, they used an aversive auditory stimulus as unconditioned stimulus (UCS). Also, they used different UCS for the two CS+ in order to stop the participants from recalling the association of $CS+_1$ and UCS_1 when presented with UCS_2. They reasoned that possible reasons for the difference between their result and above studies, who did not find an effect, may be that the association between CS and UCS was too salient in Kindt and Soeter (2011), more specifically, that the continuing measurements of expectancies may have obscured the skin conductance results. Another possible reason could be the difference in reinforcement schemes. In Kindt and Soeter (2011), 75% of CS were reinforced with UCS, as compared to 37.5% in Schiller et al. (2010), and their study (Oyarzún et al., 2012). However, the two following studies found the effect using a 100% reinforcement scheme.

The first of these studies used the same experimental design as the Schiller study, but with reacquisition as the day three-memory probe. This study found an effect of reconsolidation disruption on reacquisition day 3. Moreover, it noted that the effect of extinction on reconsolidation disruption was limited to specific genetic subgroups. Specifically, carriers of the s allele of the serotonin-transporter gene-linked polymorphic region 5-HTTLPR polymorphism and the val/val homozygotes of the functional val158met polymorphism of the catechol O-methyltransferase (COMT) enzyme were driving the effect. Carriers of these specific subgroups did show a strong return of fear if extinction was performed after 6 h, when the reconsolidation process is supposedly concluded, compared to if the extinction was performed after 10 min, during on-going reconsolidation. L/l homozygotes of 5-HTTLPR and met-carriers of COMT did not have return of fear regardless of extinction timing (Agren et al., 2012a,b). A second experiment showed the same pattern when using reinstatement as a day three memory probe (Agren et al. unpublished).

Perhaps the differing results between studies are to some extent dependent on that there are specific subgroups in which this procedure is more effective. The 5-HTTLPR have previously been associated with stronger fear acquisition (Garpenstrand et al., 2001), slower extinction (Lonsdorf et al., 2009), enhanced activity of the amygdala (Hariri et al., 2002), and development of psychopathology (Caspi et al., 2003). Moreover, by using a 5-HT1a receptor antagonist in rodents, LTP was blocked in novel, but not familiar environments, implicating serotonergic activity in memory updating (Sanberg et al., 2006). Thus, these results suggest a link between memory updating, psychopathology, and serotonergic neurotransmission.

Regarding the results regarding the COMT polymorphism, the interpretation is not as clear cut. Val/val homozygotes have a higher activity of the COMT enzyme, leading to less extracellular dopamine (Chen et al., 2004) throughout most of the brain (Hong et al., 1998). Dopamine is necessary for fear acquisition (Fadok et al., 2010), extinction (Mueller et al., 2010) and consolidation (LaLumiere et al., 2005), leaving several possibilities for the possible mechanism behind these results. However, although COMT is generally reported in terms of dopamine in psychological literature,

COMT also degrades noradrenalin, and may exert its effect during the same mechanisms disrupted with propranolol. Also, a common mechanism behind both the serotonin and dopamine results could be the regulation of signalling through interneurons in the amygdala's intercalated cells, since both serotonin and dopamine are linked to the modulation of excitatory sensory input to the amygdala, and signalling between basolateral and central nucleus, through the activation of GABA-ergic interneurons in the intercalated islands (O'Rourke and Fudge, 2006; Rosenkranz and Grace, 1999).

Lastly, a study combining psychophysiology and neuroimaging noted that extinction disrupted fear memory reconsolidation, and that the process seemed amygdala dependent. This study took place over five consecutive days. On day 1, subjects went through a session of fear conditioning in the psychophysiology lab. On day 2, subjects returned and the memory was reactivated by a stimulus presentation. As in the above studies, one group then received extinction 10 min after the reactivation, and the other group received extinction after 6 h. On day 3, a second extinction session took place in an fMRI-scanner. In the scanner, the authors did not have the possibility to measure skin conductance, but electrodes were attached and subjects believed that they were about to get shocks. On day 5, subjects were brought back to the psychophysiology lab for a session of reinstatement. At the beginning of the reinstatement session day 5, the group who had their reconsolidation undisrupted showed a return of fear, while the group who had their reconsolidation disrupted did not. Correspondingly, in the beginning of the extinction session in the scanner, the group who had their reconsolidation undisrupted showed higher amygdala activity to CS+ than the group who had their reconsolidation disrupted. This amygdala activity also correlated to skin conductance responses days 2 and 3. Also, a functional connectivity analysis showed that the area of heightened amygdala activity had significantly higher correlations to other parts of the brains fear network, i.e. insula, anterior cingulate cortex, and hippocampus, in the group with an intact memory, as compared to the group who received reconsolidation disruption. This indicates that in addition to the skin conductance responses and the amygdala activity, the group with a more intact fear memory had an integrated response over the brain's fear circuit (Agren et al., 2012a,b).

In conclusion, using extinction as a reconsolidation disruption seems to be a somewhat elusive phenomenon. It is not clear why some studies find it and others do not. Perhaps the reason is that the studies differ in yet to be discovered boundary conditions, or perhaps the reason is that the effect is most prominent in certain subgroups, and that the small sample studies are prone to variations simply because of the composition of the samples. However, it seems safe to say that the phenomenon exists, but it is still unclear during exactly what conditions.

2.2. Appetitive memories

Appetitive memories are associations between stimulus/stimuli and rewards. Appetitive memories can be induced experimentally by appetitive conditioning, a process identical with fear conditioning, with the exception that the aversive stimulus is replaced with a rewarding stimulus. Appetitive conditioning displays much of the same phenomena as fear conditioning. An appetitive conditioned response can be diminished with extinction, and cues and contexts associated with the stimulus induce reinstatement (Martin-Soelch et al., 2007). Correspondingly, drug addiction can be treated with extinction, and exposing addicts to drug cues induce drug cravings (Kaplan et al., 2011). Hence, reconsolidation of appetitive memories is as interesting for the treatment of drug abuse as fear memory reconsolidation is for anxiety treatment. Listed below are studies that examine the reconsolidation effect on appetitive memories, as well as on declarative memories related to drug abuse.

2.2.1. Propranolol

As with fear memories, propranolol has successfully been used for disrupting reconsolidation of appetitive learning in rodents (Diergaarde et al., 2006; Milton et al., 2008). This rests upon the rationale that appetitive memories are also emotionally motivated, and therefore, the involvement of noradrenergic activity in the amygdala can be expected.

Zhao et al. (2011) tested the effect of propranolol on the memory of words associated with drug abuse in heroin addicts. On day 1, heroin addicts learned a list of 30 words (10 heroin-related positive words, 10 heroin-related negative words, and 10 neutral words). On day 2, one group got propranolol and a memory reactivation, one group got propranolol and no reactivation, one group got placebo and reactivation, and one group got placebo and no reactivation. The reactivation consisted of the participant writing down the words they remembered from day 1. Memory was tested on day 3 by letting the participants write down as many words as they remembered. The propranolol group remembered significantly fewer heroin-related words as compared to the other groups. This effect was found in both positive and negative heroin-related words, but not in the neutral words not related to heroin, nicely showing a specific effect of propranolol on the reconsolidation of the memory of the emotionally valenced heroin-related words (Zhao et al., 2011).

The above study reports on the reconsolidation processes of drug related memories, but not of craving itself, which of course is of primary clinical interest. Saladin et al. (2013), in a double blind placebo-controlled study, used propranolol to manipulate the reconsolidation of drug memory in cocaine abusers. First, participants were subjected to subjective and physiological baseline measures. Then, they went through a cocaine cue exposure starting with the viewing of a 5 min video depicting cocaine use in a variety of settings. Then, in vivo cues, consisting of a small bag of simulated crack cocaine and a crack pipe for crack cocaine users, simulated powder cocaine with a mirror and razor for cocaine powder users, were presented in order to reactivate the drug use memories of the participants. During this exposure, heart rate and skin conductance were monitored, and immediately afterwards, craving and blood pressure. This exposure procedure was repeated after 15 min, after which propranolol or placebo was administered. Significantly lower drug craving scores were found in the propranolol group, as compared to the placebo group, 24 h after the reactivation, but not in a one week follow up (Saladin et al., 2013). It has been argued that reconsolidation effects should not be transient. However, if drug-dependent subjects are not abstinent, it seems natural that the memory can be reinforced by later presentations, blurring a possible reconsolidation effect.

2.2.2. Stress/cortisol

In a study using the same experimental design as the above study of Zhao et al. (2011), but with propranolol administration exchanged for the Trier Social Stress Test, which includes speaking and doing mental arithmetic in front of an audience, showed that social stress appeared to modulate the memory of heroin-related, but not neutral words, in abstinent heroin addicts (Zhao et al., 2009). Previous research in rodents produced memory impairments in morphine conditioned place preference by disrupting reconsolidation with either cold water stress or corticosterone (Wang et al., 2008), suggesting glucocorticoids as the active neurobiological agent in this behavioural manipulation.

2.2.3. Ketamine

Corlett et al. (2013) also used ketamine to modulate the reconsolidation of appetitive memories. Appetitive conditioning was performed with the distribution of three different liquids through tubes in the subject's mouth. Two of the tubes supplied fruit juices, while the third tube supplied water. Each liquid was associated with a certain stimulus resulting in appetitive conditioning to the two stimuli associated with juice. On day 2, one of these stimuli was reactivated followed by the administration of either ketamine or placebo. On day 3, memory was tested with an extinction session. Subjects rated the anticipated liking of what they thought they were about to receive. In addition, subject's anticipatory sucking behaviour was measured. The results corresponded to the fear memory results previously reported in that subjects showed increased responding on day 3 to cues reactivated during ketamine. Specifically, subject's anticipatory ratings were higher during cues reactivated during ketamine infusion, as compared to placebo. Moreover, participants applied greater sucking pressure to the cue reactivated under ketamine, but only during the start of the extinction (Corlett et al., 2013).

2.2.4. Behavioural manipulations (extinction)

Xue et al. (2012) investigated, in series of experiments, the use of extinction to disrupt reconsolidation of conditioned drug memory. They first showed that reinstatement, spontaneous recovery, and renewal of conditioned drug memories (heroin and cocaine) in rodents could be impaired with the reconsolidation-extinction process. This was then translated to humans. Abstinent heroin addicts were partitioned into three groups. After a day of baseline measurements of drug cravings, participants came back on two subsequent days for a reactivation-exposure procedure. For reactivation, they were shown a 5 min video with either neutral or drug related cues. 10 min later, subjects went through a 60 min exposure session where they were presented with heroin related cues. A control group watched the video of drug related cues and then waited 6 hbefore the exposure session. On the following day, less heroin craving was found in the reactivation + extinction group, as compared to both other groups. Remarkably, this effect was maintained on follow up measurements at 30, as well as 180, days later (Xue et al., 2012).

2.3. Procedural memories

2.3.1. Behavioural manipulations

The first time reconsolidation disruption was demonstrated in humans was in a study using procedural memories. Walker et al. (2003) had participants learn a finger tapping motor sequence on day 1. Participants who had their memory reactivated day 2, and followed by learning of a new motor task, displayed slower speed and less accuracy, than participants who did not receive a reactivation. Moreover, another group, which was tested immediately after the reactivation and new learning on day 2, did not show this effect, demonstrating that the reconsolidation process needed time before the effects could be seen. The memory reactivation consisted of a brief rehearsal of the motor sequence learned on day 1 (Walker et al., 2003).

2.4. Declarative memories

2.4.1. Behavioural manipulations

In a series of experiments, Hupbach et al. examined reconsolidation of human declarative memory. The experimental design used is again a variant on the typical three-day design. On day 1, subjects learned a list of 20 objects. Every object was visually presented and then placed in a blue basket. After all of the objects had been presented, the basket was hidden and the subject was asked to recall the objects. This procedure was repeated until 17 of 20 objects were remembered or the procedure had been repeated four times. Experimental day 2, 48 h later, one group had the memory from day 1 reactivated as follows. They were led into the same room, were shown the blue basket and asked if they remembered what they did with it and if they could describe the procedure. Then they were asked to learn a second list of item. This learning procedure differed from the first in that all objects were presented at the same time. The second group received no reactivation and were led to a novel room, where they learned the second list of objects using the new procedure. A third control group omitted day 2 entirely. On experimental day 3, another 48 h later, subject's memory of the first list was tested. The reactivation and no-reactivation group did not differ in number of items recalled, but the reactivation group did significantly more often falsely place objects of the second list in the first list. The authors argue that this is a result of the reactivation rendering the memory of the first list labile and hence, suffering from intrusions of the second list. Then they convincingly show in a second experiment, that if the memory of the first list is tested directly after the second list is learned, this effect is missing. This suggest a time-dependent influence of the learning of the second list on the first list, in that the reconsolidation process must be allowed to conclude before the memory of the second list can intrude on the memory of the first list (Hupbach et al., 2007). In another study, using the same design, the specifics of the reactivation were varied in order to examine the boundary conditions of reactivations that initiate reconsolidation processes. Groups were exposed to only one component of the previously used reminder, either the same experimenter, the same context, or retrieval. The context alone created the same effect as in the previous study, but not the experimenter or the retrieval. It would seem that exposure to the context was critical for memory reactivation. They then proceeded to an experiment where one group mentally imagined the learning context, while another group were briefly re-exposed to it. However, these manipulations did not produce an increase in intrusions of the second list to the same degree as subjects who learned the second list in the original learning context (Hupbach et al., 2008). A later study in 5-year olds expanded on these results, showing that context was critical as a reminder in novel context, but not in highly familiar contexts. Instead, the other components of the reminder became effective (Hupbach et al., 2011). Also, the same research group reported the effect also for source memory, using a variation of this experimental design (Hupbach et al., 2009). Furthermore, an instruction to forget the first list seemed to protect it from intrusions caused by the encoding of the second list, but only when the instruction was given before the second encoding. This suggests that the attempted forgetting somehow quarantined the memory from intrusions from the second list, possibly through affecting reconsolidation processes (Hupbach, 2013). However, others have pointed out that these intrusions of items from one list on another can be explained without the concept of reconsolidation. Specifically, that the temporal context model (TCM), which claims that items are encoded together with the context in which they are presented, also can predict the results of these studies. According to the TCM, the day 2 reminder activates the context of the day 1 encoding, with the effect that this context also becomes associated with the day 2 items. In this way, subjects that get a reminder become more prone to misattributing day 2 items to day 1 (Sederberg et al., 2011). This prediction has since gained support in a study using fMRI (Gershman et al., 2013). Still, the studies showing these intrusions did not show an effect immediately after day 2 encoding, that is, the day 2 encoding must consolidate before the impact of the context reminder can create the intrusion effect. Thus, if the TCM explanation is accepted, this makes the effect one of consolidation and not reconsolidation.

Schwabe and Wolf (2009) tried to disrupt the reconsolidation process of autobiographical memories. On day 1, participants completed an autobiographical memory test asking them to remember episodes of their life within the past week. Specifically, they were asked to associate events to six adjectives, two positive, two neutral, and two negative. One group performed this reactivation of events after which they read the story "War of the Ghosts", famously used in Bartlett's classic study on memory malleability (Bartlett, 1932), in order to disrupt the reconsolidation of the autobiographical memories. Three other groups performed only the reactivation, only read the story, or did nothing, respectively. At a memory test, one week later, the reactivation + interference group remembered significantly less details of the neutral events, but there were no difference in positive or negative events. Perhaps because of the emotional memories being stronger and more resistant to change, as a result of the effect of components of the stress reaction on consolidation (Schwabe and Wolf, 2009). In another experiment, participants were asked to memorize a set of 24 pictures on day 1. Day 2, two groups had their memories reactivated by sitting down quietly and to think of the pictures presented on day 1. One of these groups then memorized a second set of 24 pictures, while the other group did not. One additional group got no memory reactivation, but still learned the second list of pictures. Yet another group omitted day 2 entirely. On day 3, memory was tested by free recall. This experiment was also performed with memory testing 7 and 28 days after the original learning, making it a total of twelve experimental groups. The one-day-interval test showed a main effect of interference, regardless of if a reactivation had been performed or not. At the 7-day interval test, the reactivation + interference group did remember less, suggesting a reconsolidation effect. However, the 28-day interval test did not show any reconsolidation effect. Instead, the group which received only a reactivation performed better than the other three groups, and the group which received only interference performed worse than the other three groups. These results are not so clear cut, but suggest a possible time dependence on the reconsolidation effect of memory (Wichert et al., 2011). Another study, using the same methodology, examined if single or multiple reactivations made the memory of the set of pictures stronger. This experiment had a seven-day time interval between experimental day 1 (encoding) and experimental day 2 (reactivation and manipulation). In this time interval, subjects were asked to retrieve the memory of the original learning once, three times, or not at all. There was one day between subsequent retrievals. With no reactivation before day 2, the reactivation + new learning group remembered fewer pictures on the memory test on experimental day 3, showing an effect of reconsolidation disruption. With one reactivation before day 2, that effect was not present. However, an effect of reconsolidation disruption could not entirely be ruled out, because new learning after retrieval decreased memory performance, but not for pictures that were not retrieved on day 2. Finally, two previous reactivations produced similar results as one. In conclusion, repeated reactivations was found to strengthen memory, but perhaps not render it invulnerable to reconsolidation disruption (Wichert et al., 2013a). A similar experiment, also using the memory of a set of pictures, examined whether the strength of new encoding after the reactivation had an impact on the original memory strength. Consequently, on day 2, groups differed in how many times day they were allowed to try and learn a new set of pictures after the reactivation of the picture set from day 1. The groups who learned a new set three times (strong encoding) differed in memory strength on day 3. The group who had received a reactivation had significantly weaker memory of the original list, thus showing an effect of reconsolidation disruption. This difference was not present between the groups that had learned the new set only once (weak encoding), thus implicating the strength of the new learning as a factor that may be important for its ability to disrupt reconsolidation (Wichert et al., 2013b).

Strange et al. (2010) reasoned that since emotional memory is critically dependent on the amygdala (LeDoux, 2000; McGaugh, 2000), emotional faces, which reliably activate amygdala, might be able to affect the reconsolidation of memory. Indeed, fear reactions, which can be produced by the presentation of fearful faces, are known to affect consolidation. Participants were presented with 400 nouns on day 1 and, for each noun, had to answer if this noun described a living or a non-living entity. On day 2, participants returned and had their memories reactivated by a retrieval task. Specifically, they were presented with stems of the previously encoded nouns and were asked to complete them and say them out loud. Some of these stems were followed by pictures of faces (40 neutral and 40 fearful). On day 3, memory was tested with the same procedure as on day 2, although without the presentation of any faces. Memory for nouns that were followed by a fearful face was significantly decreased on day 3. When emotional nouns were used in combination with fearful faces the effect became stronger. This memory decrement was persistent, i.e. lasted a week, and critically time-dependent, because the memory decrement did not occur if the test followed directly upon reactivation day 2, thus nicely showing an effect of reconsolidation disruption (Strange et al., 2010). Considering the influence emotional content and fear reactions have on consolidation, one would expect that memory would be enhanced, instead of decremented, by the fearful faces. The authors consider this, and suggest that these emotion-induced impairments are mediated by an amygdala-dependent adrenergic release, which boosts the memory of the fearful face while corrupting the pre-existing memory showed in conjunction with it.

Chan and Lapaglia (2013) performed a series of experiment on the reconsolidation disruption of declarative memory. On day 1, participants watched a movie of a fictional terrorist attack. On experimental day 2, one group had their memory memory reactivated using a memory test concerning specific details of the terrorist attack. The control group instead received a distractor task. Both groups were then presented with new learning containing misinformation concerning details of the terrorist attack as well as neutral items. Five minutes later the memory was tested in a recognition memory test. When new learning followed a memory reactivation, as compared to no reactivation, memory was weaker for both misinformed items and neutral items. This effect was not present when 48 h separated the reactivation and the new learning, demonstrating that the memory disruption was a time dependent process. In contrast, separating experimental day 1 and 2 with 48 h left the effect intact. They also constructed a source-free experiment in order to rule out the possibility that their result was a product of source confusion. This was done by having a recognition test on day 3, where participants responded "old" if the information presented was from day 1 or day 2, and "new" if the information was new. Still the effect remained for both neutral and emotional items. In another experiment, they presented the same "misinformation items", but they related to another unrelated story about drug trafficking. This removed the effect, suggesting that new learning must compete with the old memories for a memory disruption to occur. It is worth noting that all of the experiments above found results when memory was tested on experimental day 2, only 5 min after the new learning. The memory testing is thus made during reconsolidation and is at odds with the reconsolidation hypothesis, stating that results of reconsolidation manipulation should be seen only when reconsolidation is concluded and not immediately after the manipulation (Nader et al., 2000; Walker et al., 2003). However, in a last experiment, memory testing was made on an experimental day 3, 24 h after day 2, and the effects remained (Chan and Lapaglia, 2013).

Forcato et al. have used another, somewhat roundabout, way to test the reconsolidation effect of declarative memories. The retrieval-induced forgetting (RIF) is the phenomenon on how retrieval of a memory can have the effect of making it harder to subsequently recall other similar memories. The authors argue that for this effect to be intact, the retrieved memory inducing this effect must be intact and that the absence of the RIF effect is an indicator of defects of the RIF-inducing memory. Hence, the memory tests in some of their reconsolidation experiments tests if a memory is able to induce RIF or not. Subjects memorized two lists of pairs of syllables with corresponding different contexts, consisting of coloured light and music. Subsequent memory tests involving the list presented one of the syllables in a pair and the subjects were to fill in the other syllable of the pair. By combining the different contexts and syllable lists with the typical three day design, the authors showed a reconsolidation effect, as indicated by the lack of RIF, when a second list was learned 5 min or 6 h after a memory reactivation, but not 10 h after. The reactivation trial consisted of presentation of the context belonging to a certain list and the first half of a syllable pair from the list, although the subjects were not allowed to try and write down the other syllable of the pair (Forcato et al., 2007). In a follow-up study using a similar methodology, again using the RIF effect, they investigated which components of the memory reactivation that was vital for producing the effect. They found that changing the reactivation trial to just the corresponding context, or adding a presentation of the answer syllable, failed to produce the effect, but using the same reactivation as in the previous study still produced it (Forcato et al., 2009). In yet another study, for one group, the reactivation day 2 consisted of a verbal instruction to add three more syllable pairs to the list learned on day 1. For another group the instruction was just to learn three more pairs of syllables. Two control groups received no reminder at all, and a reminder including also the presentation of the corresponding syllable, respectively. The group which were instructed to include the new syllables into the previously learned list produced fewer errors in the memory test day 3. The authors argue that this is an example of the updating of a previous memory through reconsolidation processes (Forcato et al., 2010). This method was also used when the same group tested whether several reactivations would strengthen the memory. They found that two or more reactivations, delivered 5 min apart did strengthen the memory when tested on day 3, but only if the reactivations used were of the structure described above, where context and one half of a syllable pair were presented. If both halves of the syllable pair were presented (retrieval), the effect could not be produced. Moreover, the effect only appeared when after concluded reconsolidation on day 3. Direct tests on day 2 revealed no effect of repeated reactivations, in line with the reconsolidation hypothesis. Also, if the subsequent reactivations took place after concluded reconsolidation, that is, one reactivation day 2 and then an additional reactivation day 3, there was no effect (Forcato et al., 2011). Moreover, the memories strengthened by repeated reactivations became more resistant to interference from a second task. However, this effect seemed to be time dependent, as this was found in three-day old memories, but not eight-day old memories (Forcato et al., 2013).

The above mentioned effect that repeated reactivations did strengthen memory when they were presented within 5 min or 2 h from each other, but not 24 h, raises an interesting question. Can several reconsolidation processes for the same memory run in parallel? If so, how can a reconsolidation process be disrupted by a process like extinction? Wouldn't the repeated presentations just trigger several parallel reconsolidations? It is perhaps easier to accept that repeated reactivations, with short intervals within the reconsolidation window, do not start new reconsolidation processes, but perhaps affect and modulate the on-going reconsolidation process.

Finn and Roediger (2011) studied the effects of post-retrieval stimuli on subsequent memory. Participants studied 10 lists of 10 pairs of Swahili-English vocabulary words each. After studying 10 pairs, participants turned to multiplication problems for 1 min. This procedure was intended to "flush out" any effect of short-term memory. Then they took a memory test for the learned pairs. After a successful retrieval, either a blank screen, a neutral picture, or a negatively valenced picture, was shown for 500 ms. After an unsuccessful retrieval, either a blank screen or a neutral picture was shown, but never a negative picture. After this, and another 1 min of multiplication problems, a recognition test was performed with the pictures used earlier, in order to ensure participants attended to the pictures. This was repeated for all 10 lists. After all of the study cycles, participants were given a final test on all 100 Swahili-English words. It was found that participants remembered more vocabulary words that were followed by negative picture, than words followed by a blank screen or neutral picture. This effect remained in a follow up experiment where there was a delay of 2 s after the word pair and the presentation of the pictures. When the experiment was repeated without the initial study test, where instead word pairs were simply presented and then followed by pictures regardless of successful retrieval, the effect did not remain (Finn and Roediger, 2011). In a follow-up study, it was investigated whether presenting the emotional image before the retrieval could produce the same effect, but this was not so. Furthermore, memory was also strengthened when negative pictures were presented after an unsuccessful retrieval (Finn et al., 2012). These two papers do have the word "reconsolidation" in their title, but it is debatable if they really demonstrate effects of the reconsolidation process, because the memories are not allowed to consolidate before reactivation and testing. This makes it impossible to separate effects on consolidation from reconsolidation. It would be in line with consolidation theory that the time-dependent pairing of stimulus and an emotional picture would strengthen the memory of the picture. Memory is however also tested within the probable consolidation interval, so perhaps the presentation of the pictures does not affect the consolidation, but are part of encoding. Moreover, if we are to call this effect reconsolidation we must accept that reconsolidation must be able to be induced in non-consolidated memories. It would be interesting to see these experiments performed over a larger time span.

2.4.2. Propranolol

In a study testing the memory of an anxiety evoking autobiographical event, no effect was found by using propranolol to disrupt reconsolidation in conjunction with a retrieval session. On day 1, participants were asked to write down a negative disturbing event that triggered anxiety. When participants returned on experimental day 2, a week later, personalized emotional scripts had been created from the written events. Participants listened to them after being treated to propranolol, placebo, or cortisol. On experimental day 3, another week later, emotional ratings as well as physiological reactions were tested (Tollenaar et al., 2009a). Also, no effect of propranolol was found when the memory of word lists were tested (Tollenaar et al., 2009b). Regarding the negative find considering the memory of the emotional scripts, the authors argue that possible reasons for the negative find could be that the emotional scripts perhaps did not have enough emotionality for propranolol to have an effect, or that the dosage of propranolol may have been too low, or perhaps was not acting long enough in the body. However, the psychophysiological measures show emotional reactivity to the personalized script and the dosage of propranolol as compared to other studies are adequate. Perhaps, one could also argue that the multitude of tests participants performed during day 2, including an attention test, word lists memory tests, as well as several computer-based

questionnaires during a period of 2 h, produced a significant cognitive load, and as such, lead to the tests influencing each other's reconsolidation.

Schwabe et al. (2012) performed a neuroimaging study on the effect of propranolol on the reconsolidation of the memory of emotional and neutral pictures. On day 1, participants were presented with 50 pictures (25 neutral and 25 negative). No neuroimaging was performed on day 1. On day 2, participants received either placebo or propranolol and either a memory reactivation or no memory reactivation, thus making four experimental groups. The neuroimaging in day 2 consisted of two resting state scans. Before the second scan, participants who were to receive a reactivation were instructed to try and remember as many pictures as they could during the second scan. Analysis of day 2 neuroimaging data showed significant activations in amygdala and hippocampus in the reactivation condition as compared with the no reactivation condition. On day 3, the original 50 pictures were mixed with 50 new pictures and a recognition memory test, where subjects responded "new" or "old" to every picture, was performed in the fmri-scanner. Subjects who received both propranolol and a reactivation remembered fewer negative pictures than the other three groups, but not neutral. Thus, an effect of propranolol on the memory of negative pictures was demonstrated. When analysing the neuroimaging data from day 3, increased activity in the amygdala and hippocampus was found in the propranolol + reactivation group as compared to placebo + reactivation group, when using the contrast of correct responses to negative pictures to incorrect responses to negative pictures (Schwabe et al., 2012). Since amygdala activation usually is connected to fear reactions it would perhaps have seemed natural if the group with stronger memories of the negative pictures would have displayed increased amygdala activation. However, the authors suggest that perhaps the act of remembering the negative pictures demanded greater effort for the group with weaker memories and thus, activated amygdala and hippocampus more.

Kroes et al. (2010) tested the impact of propranolol on the memory of word lists. On day 1, participants were exposed to 360 nouns (300 neutral, 30 perceptual oddballs and 30 emotionally aversive) and were asked to indicate if the noun described a living or non-living entity. On day 2, one group received propranolol and one group placebo. Both groups then had their memory reactivated by being presented the first three letters of 240 of the 360 nouns encoded on day 1 (200 neutral, 20 perceptual oddballs, and 20 emotionally negative) and trying to complete the words that were encoded day 1. Day 3, the same memory test employed to reactivate the memory day 2 was performed, but the three first letters of the full 360 nouns were shown. The propranolol group completed fewer emotional nouns on both day 2 and 3 (Kroes et al., 2010). Since the weakening of memory took place already at day 2, this result differs from other propranolol studies and is not as clear-cut a demonstration of reconsolidation disruption.

2.4.3. Stress/cortisol

In the study by Tollenar et al. that used propranolol to modulate the reconsolidation (see above for a description of the experimental design), another experimental group was instead administered cortisol. Cortisol was found to decrement word list memory on the immediate test on experimental day 2. Moreover this effect remained at experimental day 3, a week after experimental day 2 (Tollenaar et al., 2009b). Contrary results were produced when Marin et al. (2010) used psychosocial stress in the form of the Trier Social Stress Test in an attempt to influence reconsolidation. They let participants watch a story depicted in a slide show during day 1. The slide show had both neutral and emotional content. On experimental day 2, 48 h later, two groups were asked to recall the story. One group then were exposed to stress, while the other was not. A third group did not reactivate the memory, but were exposed to stress. An immediate memory test revealed that the reactivation + stress group had significantly improved memory as compared to the reactivation + no stress group, but only for emotional memory. This effect did not remain significant at a memory test experimental day 3, five days later. Remarkably, the reactivation + stress group had markedly improved memory over the no reactivation + stress group at the immediate test and this effect also endured until experimental day 3 (Marin et al., 2010). In another study, Hupbach and Fieman (2012) had participants memorize a scientific text passage on day 1. On day 2, one group was exposed to the cold pressor test (CPT), while a control group instead submerged a hand in warm water. Immediately after this, they were asked to recall what they learned on day 1. Memory was then tested on day 3. Cortisol levels from the CPT predominantly increased in male participants, which corresponded to increased memory at day 2, which were maintained into day 3 (Hupbach and Fieman, 2012). These studies all show immediate effects of stress on memory after administration day 2. It would appear this is one way in which the effect of stress and propranolol administration on memory differs. The following studies did not include an immediate memory test and hence, do not increase our knowledge in the matter.

In a study using the same design as Hupbach et al. (2007), the impact of stress, in the form of the Trier Social Stress Test, on the reconsolidation was further examined. When subjects were stressed before the reactivation session day 2, there was no difference in memory intrusions between lists as compared with subjects who were not stressed. However, when subjects were stressed after reactivation and new learning, they showed fewer memory intrusions between lists. Thus, it appeared components of the stress reaction either had strengthened the original memory or weakened the new learning (Dongaonkar et al., 2013).

Coccoz et al. used the same general experimental design as Forcato et al. (2013), and the same lists of syllable pairs and reactivation. On day 1, participants learned a list of syllable pairs. On experimental day 2, 6 days later, two groups received the reactivation and followed by a cold pressor test, in order to induce a stress reaction. The memory of these two groups was tested 24 h and 3 h after the reactivation, respectively. Another group instead held their hand submerged in warm water following the reactivation. An additional control group received neither reactivation nor manipulation. The group who received a cold pressor test and were tested 24 h after the reactivation had significantly stronger memory than the warm water group and the no manipulation group, also tested 24 h after the reactivation, and the other cold pressor group, tested 3 h after the reactivation. Thus, a cold pressor test enhanced memory through affecting the reconsolidation process, and that effect could only be seen after reconsolidation was concluded (Coccoz et al., 2011). A second study replicated this effect for 7-day old memories, but not for 21-day old memories, suggesting that the enhancement of memories, using components of a stress reaction, may only be possible within a certain interval of time (Coccoz et al., 2013).

2.4.4. Glucose

The above study of Coccoz et al. also used glucose for reconsolidation modulation. Using glucose, a strengthening effect on memory could be found 21 days after the original training, when memory had been reactivated and glucose had been administrated at day 20. This effect was found in spite of the fact that the control groups for memory performance at day 20 and day 21 showed almost complete forgetfulness. The authors conclude that reconsolidation processes can be induced, even for memory that is not consciously available (Coccoz et al., 2013).

3. Discussion

3.1. What triggers a reconsolidation process?

A central issue in the study of reconsolidation processes is under what circumstances a state of labilization followed by reconsolidation of a memory can be induced. In order to decide what instances of memory enhancement and erasure that is caused by a reconsolidation phenomenon, it is vital to understand what really characterizes the reactivation of a memory. In the research reviewed above, different procedures have been claimed to reactivate memories, and initial steps have been taken to try and find the boundary criteria for reactivations that can produce memory reconsolidation. Early work in rodents, disrupting reconsolidation through post-reactivation electroconvulsive shock, stated that it was enough with a single element of the original memory (the stimulus itself, the context in which the stimulus was presented, the internal context of arousal) to trigger a reactivation (Spear et al., 1973), but when considering the results from human studies, the matter seems more complicated.

In fear conditioning, compelling arguments state that a reactivation needs to include a prediction error to induce memory labilization and reconsolidation, that is, that the presence of novel information provides a reason to update the original memory (Díaz-Mataix et al., 2013; Sevenster et al., 2013, 2012). Let's for a moment accept the premise of prediction error as a necessary condition to initiate a reconsolidation process. This means that the studies that have shown effects of reconsolidation modulation, with following decrement or enhancement of memory, must somehow have induced a prediction error. In fear conditioning studies, when an unreinforced stimulus presentation is used for memory reactivation, this is straight-forward, because after the initial fear conditioning the participants expect a reinforced stimulus (Agren et al., 2012a,b; Kindt et al., 2009; Schiller et al., 2010). Moving to the clinical studies on PTSD, the matter is more complicated. Brunet's studies used a re-telling of the initial trauma as a reactivation of the traumatic memory. Does this include a prediction error? Perhaps, for example if the patient has never re-told the trauma to anyone other than close friends and relatives, then the experience of re-telling in a clinical setting may not meet the expectation the patient had. The emotional arousal of the experience may be better or worse than expected. This could constitute a sort of emotional prediction error. Also in the case of phobics, one could reason that some of the cognitive or affective consequences envisioned by the patient will be lacking at a presentation. Again, this might happen both if the patient become more or less scared than anticipated. A phobic generally avoids exposure to the phobic stimulus and it is therefore likely that the actual response will somewhat differ from the anticipated response when forced to confront a phobic stimulus. Thinking about it this way, it seems improbable that retrieval in clinical studies would be totally devoid of some sort of prediction error.

However, what about the studies of reconsolidation of declarative memories? The reactivation method most often used in declarative memory reconsolidation studies is retrieval. Surely all kinds of retrieval could not include a prediction error. So if prediction error is needed, the studies using retrieval as a means of reactivation would yield different results. Hupbach et al. pinpointed the context for retrieval as a very important aspect of a reactivation (Hupbach et al., 2008). It seems reasonable that subsequent learning in the same environment is viewed as information that ought to be included in, or tied to, the original memory, but surely retrieval in the original environment does not produce a prediction error. Consequently, we are left with three alternatives. Different reactivation procedures are needed for different kind of memories, i.e. fear memories and declarative memories; prediction error is not a necessary condition for reconsolidation processes to occur, or the processes we are studying regarding declarative memories are not reconsolidation processes, but some kind of retroactive inference. The studies on declarative memory reviewed here present a mixed bag of results: that retrieval must take place (Strange et al., 2010), that it does not have to take place (Hupbach et al., 2008), and that it cannot take place (Forcato et al., 2009). Clearly, this matter is not concluded and must be further examined.

Recent results in rodents, claiming that memory modulation can be achieved also when reactivation follows manipulation (Baker et al., 2013) questions the very concept of reconsolidation disruption. Indeed, how can the reconsolidation of a memory become disrupted, if it has not been reactivated? This study leaves us with two alternatives. Either the concept of reconsolidation is presently poorly described, or in this case the manipulation served as a reactivation and the reactivation served as a manipulation. This is not inconceivable, although a single trial is a short extinction indeed. To answer these questions, it is important to try and replicate these results with other types of memory, as well as translating them to humans. For example, can a manipulation, which does not in itself contain a predication error, be followed by a memory reactivation and still modulate a memory?

3.2. One memory or several?

Most studies claim that a memory is reactivated, although what is meant by a memory varies widely between studies. Fear and appetitive conditioning produce simple associations between stimuli that are claimed to be reactivated by a single presentation of a certain stimulus. With declarative memories, it is more complicated. For example, when claiming to reactivate the memory of a word list, it is presupposed that the presentation of one or several instances of this list will reactivate the memory of the entire list. Otherwise the effect of reconsolidation modulation would only be observed on items remembered at the reactivation, since it would mean that every retrieval during the reactivation would trigger a separate reconsolidation process. Indeed, in some studies, this has been the case (Strange et al., 2010). However, considering that word lists, autobiographical memories, and memories of traumatic events have been modulated, at this point it would appear that memories can be reactivated vicariously through other memories. But why then is not the reactivation of one out of two conditioned stimulus also activating the other (Schiller et al., 2010), especially when they are both in the same category of pictures (Kindt et al., 2009), and there is some evidence of generalization of the effect on fear between pictures in the same category (Soeter and Kindt, 2011).

3.3. Retrieval or storage?

As in all memory research, it is discussed if the enhancing and attenuation of memories through reconsolidation processes are an effect of storage or retrieval processes. One study shows that memories that are not able to be consciously retrieved still can be the target of a reconsolidation process, which would indicate that, at least in this particular study, the ability for retrieval was affected, and not the storage (Coccoz et al., 2013). It is however, at present time, more or less impossible to show storage failure experimentally. No matter how many times a memory cannot be measured, one can always claim that this is because failure of retrieval and not storage.

4. Conclusion

In conclusion, there is now ample evidence that reconsolidation takes place in humans. However, in the reviewed studies

there is some discrepancy in what researchers view as reconsolidation. For example, some studies claim that the modulation of reconsolidation can be measured immediately after manipulation, while the majority of researchers deem the time-dependency of the reconsolidation process an integral part of the reconsolidation hypothesis. Moreover, there is controversy over what circumstances that trigger a labilization and reconsolidation process. In simple fear and appetitive memories, it would seem that prediction error at the instance of reactivation is vital, but this hypothesis becomes harder to defend when dealing with declarative memories and more complex emotional memories. When dealing with declarative memories, does prediction error matter? Does retrieval matter? With how few elements can a large complex of memories become activated? How durable are the enhancements and attenuations of memory produced? Does it differ between different kinds of memories? All in all, the present batch of studies has provided a wonderful set of questions that will keep us busy for years to come.

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