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Effects of pharmacological and non-pharmacological interventions in the reconsolidation of human emotional memories: a pilot study

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Abstract

Until recently it was believed that emotional memories become stable in the long-term memory (LTM), a process called consolidation. It was believed that, once these memories were changed, these memories would last forever. Memories can become accessible again via reactivation of the consolidated memory trace. This process is called *reconsolidation*, in which the consolidated memories are recalled and again actively consolidated. Reconsolidation is about influencing memories from the long-term memory with the goal of maintaining, strengthening and modifying them. Based on literature present in this study, two hypotheses were stated. The first hypothesis of this study was that using pharmacological or non-pharmacological interventions to disrupt the reconsolidation process will have a strong diminishing effect on fear expression of people with anxiety and stress related disorders. The second hypothesis of this study was that the pharmacological interventions for disrupting the reconsolidation process will have a greater effect size than the non-pharmacological interventions. For the analysis of the results a random-effects model, mixed-effects model, average effect size, moderator analysis and heterogeneity were computed. Based on the results, the first hypothesis was accepted. Based on the results, the second hypothesis was rejected.

Introduction

Memories can be hard to forget, especially emotional ones (Comblain, D'Argembeau & Linden, 2005). How the emotion is remembered, is influenced by its duration and the amount of arousal involved (Berntsen, 2001). If an emotion, like fear for example, is highly arousing, it can lead to a higher sensitivity to fearful situations (Eysenck, 1979; Orr et al., 2000). An example of an extreme reaction to fear concerns the Post Traumatic Stress Disorder (PTSD), in which negative emotions relating to a traumatic event are relived again (Davis, Falls & Gewirts, 2000). An additional example would be anxiety disorders, which show a strong relationship with emotional memories (Franklin & Foa, 2011). Fearful stimuli relating to the emotional memory can trigger anxiety responses over time (Lissek et al., 2005). Fearful memories can be the result of earlier learning experiences (Rachman, 1977). When someone

has learned to fear a certain stimulus, he or she can develop a response pattern in which he or she expects the earlier negative outcome when confronted again with the fearful stimulus. The original stimulus is fearful for this person. The original stimulus can be neutral; in the person with an anxiety disorder, this neutral stimulus can become conditioned to a negative experience, therefore becoming a conditioned stimulus (CS). This response, i.e. that a neutral stimulus can become conditioned to a negative experience and becomes a conditioned stimulus, can be found in people with anxiety disorders (Kindt, 2014). The initial unconditioned stimulus (US), the negative event, becomes associated with the CS. A person with an anxiety disorder has had a negative experience with that particular stimulus; as a consequence, the initial unconditioned stimulus (US), i.e. the negative event, becomes associated with the CS. Furthermore, a link is created between CS and US, in which the originally neutral or ambiguous stimulus (CS) becomes a predictor for a negative experience (US); the feared stimulus, i.e. the negative event, has a negative valence through its association with the negative consequence (US) (Baeyens & Houwer, 1995; Herman, Vansteenwegen, Crombez, Baeyens & Eelen, 2002). If repeated exposure to the CS is then repeatedly involved with a positive or neutral experience, the conditioned response can be extinguished. This is the response, which is shown by the person with an anxiety disorder to the CS. This relationship between anxiety disorders and emotional memory was found in clinical studies about exposure therapy (Franklin & Foa, 2011). Fear-conditioning procedures can also be used for discovering the roots of anxiety pathogenesis. Exposure therapy is based on the experimental model of fear extinction (Franklin & Foa, 2011). This model may help diminish symptoms relating to fear, like in PTSD and OCD for example. In several clinical studies on exposure therapy, these disorders showed positive results in that the fear diminished (Franklin & Foa, 2011; Foa, 2011; Ougrin, 2011). Next to reliving the experience, also beliefs about it can be changed. Repeated exposure when reliving the experience can diminish fear. As a consequence, the beliefs about the experience can also change. This is the basis for cognitive behavior therapy (CBT), in which both the fear and the beliefs about the experience can be changed. When used as an intervention for PTSD and OCD, CBT also showed positive results in that the fear diminished and the beliefs about the fear stimuli were changed positively (Rachman, 1989; Mystkowski, Mineka, Vernon & Zinbarg, 2003, Ougrin, 2011).

More recently, researchers have shown interest in possibilities to influence the emotional memory itself. Until recently it was believed that emotional memories become

stable in the long-term memory (LTM), a process called consolidation. It was believed that, once these memories were changed, these memories would remain the same forever (Dudai, 2004; Bramham & Messaoudi, 2005). Memories can also become accessible again via reactivation of the consolidated memory trace. This process is called *reconsolidation*, in which the consolidated memories are recalled and again actively consolidated (Tronson & Taylor, 2007; Riccio, Millin & Bogart, 2015). Reconsolidation is about influencing memories from the long-term memory with the goal of maintaining, strengthening and modifying them (Tronson & Taylor, 2007). The reconsolidation process helps in the facilitation of changing the emotional memory. Hence, it could also help change fearful memories into less fearful memories (Dudai, 2004).

The possible treatment of anxiety disorders and stress related disorders by means of the reconsolidation processes is applied in different ways. First, the memory of the traumatic event is triggered and reactivated. Then medication, like propranolol, is applied to block memory reconsolidation (Kindt, Soeter & Vervliet, 2009). Also, a behavioral intervention like CBT can be applied with the goal to update the memory and ensure extinction. The medication or behavioral intervention does not have to be applied directly after the traumatic event in order to provide the opportunity for change in the reconsolidation process. This is a great advantage in comparison to applying exposure therapy or CBT, since CBT has the goal to diminish the fear response and the reconsolidation process gives an opportunity to change the source of the fear: the emotional memory itself. For example, Kindt et al. (2009) showed that administering propranolol during the reconsolidation process helped diminish fear. Since the fear is based on a learned link between CS and US, the expectancies relating to the US remained, even though the fear response diminished. A later study (Soeter & Kindt, 2015) delivered similar results. Brunet et al. (2002) were the first to use the disruption of reconsolidation in PTSD patients. The patients had to provide upfront a written statement about the event that caused PTSD. This written statement was used in the study as a trigger to reactivate the memory of the event. The patients were treated with propranolol in order to disrupt the reconsolidation of the reactivated memory. Also a control group was used, which did not receive propranolol but a placebo. The treated patients reported a vast amount of symptom improvements (Brunet et al., 2011). This was consisted with the findings of a meta-analysis by Lonergan, Olivera-Figueroa, Pitman and Brunet (2012), which showed also promising results in reducing emotional material in healthy subjects after administering propranolol to disrupt the reconsolidation process.

However, applying pharmaceuticals to humans can have ethical problems. Moreover, in specific anxiety disorders, like PTSD, results are not always consistent when using propranolol or sort like agents (Wood et al., 2015). Moreover, also non-pharmacological techniques were developed in parallel with pharmacological ones (Schiller et al., 2010). Schiller et al. (2010) held the premise that reconsolidation is an adaptive update mechanism, which can incorporate new information into old memories. If new information is introduced during the reconsolidation period, it should be possible to change the fear memory permanently. This was confirmed in the study of Schiller et al. (2010) in using a non-invasive technique. The fear responses were no longer expressed as a consequence. The effect was specific for the fear memory and lasted for over a year. In other words, the reconsolidation manipulation of emotional memories can have limitations, which are widely researched (Agren et al., 2012).

Although a lot of research has been conducted on the topic of reconsolidation, not all questions can be answered as posed by the individual studies. Since the individual studies often involve a specific type of patients or explicitly defined interventions, it is not possible to answer questions about for example the consistency of the effect of reconsolidation in general. A selection of studies in which such characteristics differ can allow investigation on questions relating to the consistency of the effect of reconsolidation. However, there has not been a meta-analysis of these studies and the effects of the pharmacological and non-pharmacological reconsolidation methods. The goal of this study is to provide such a meta-analysis. Both effects for pharmacological and non-pharmacological (behavioral) reconsolidation techniques were analyzed, so that the most effective method can be determined.

The following hypotheses were researched:

H1: Using pharmacological or non-pharmacological interventions to disrupt the reconsolidation process have a strong effect in terms of diminishing fear.

H2: The pharmacological interventions for disrupting the reconsolidation process have a greater effect size than the non-pharmacological interventions.

Methods

In order to find relevant literature for the meta-analysis, the search engines PubMed and PsychInfo were used. To remove duplicates from the search results, the database Endnote was used. Two researchers scanned both titles and abstracts to determine the eligibility of the articles for this research. In the case of missing information, the authors of the articles were to be contacted, but due to time limitations, this was not possible. In case of disagreements about the articles, the researchers discussed the articles until consensus was reached.

Search strategy and extraction of data

For conducting the meta-analysis, the methodology used by Lonergan et al. (2013) was followed. The chosen studies were in agreement with inclusion criteria as stated by the researchers and supervisor, namely: a publication date between 1 January 2000 and 15 November 2015; the article should at least have the status of online publication; the article should have been written in English; the article should have mentioned both the reconsolidation process and manipulation; the article should have included human participants.

For searching relevant literature, the following terms or combination of terms were used: reconsolidation, emotions, memory, manipulation, extinction, propranolol, condition, amnesia, updating, not animals, humans. Pubmed delivered 1791 articles; PsychInfo delivered 423 articles. In the case of an unclear abstract, the whole article was read. The supervisor and researcher chose the selection criteria as stated in Figure 1.

In total 62 articles met the inclusion criteria, but 15 of these had to be discarded because they did not meet all inclusion criteria. Population type (clinical versus non-clinical), subject design, population sample, mean and standard error were reported for each article. Data for the articles were extracted in one of the following ways: text, plots or tables. The dependent variables measured the change between the manipulated and original memories; for the dependent variables only standard deviations were calculated. In the second check, information in the articles about the types of memories, the duration of the reconsolidation effect and the exact data source, were included. The final number of articles was 47.

Statistical analysis

Statistical analyses were conducted in R, after which effect sizes were computed using R package in terms of random and mixed effects models; the package was used to calculate and analyze the results (Viechtbauwer, 2010). Significant levels were chosen at the alpha .5 level.

The random effects model was chosen for the first analysis. This model is also called the variance components model and is a kind of hierarchical linear model (Borenstein, 2009). The model assumes that the data being analyzed consist of a hierarchy of different populations (Borenstein, 2009). The random effects model was chosen for several reasons, namely due to the different participants, different ways of conducting the studies and large assumptions in variations (Borenstein, 2009). The individual results for the dependent variables in the studies were used for the first meta-analysis.

For the second, the average effect size of the studies was used. The effect size is a quantitative measure of the strength of a phenomenon. To obtain a single measurement for the analysis, measurements were averaged, thereby following the example of Lonergan et al. (2013).

After this, a mixed effect model with all effect sizes was used for the third meta-analysis, in which both random and fixed effects were included.

A moderator analysis was conducted in the fourth meta-analysis. The mean effect of the studies using pharmacological versus non-pharmacological was compared. It was assumed that one or more moderator variables influence the relationship between the application of the treatments and the effect of disrupting reconsolidation.

The last meta-analysis was conducted to compute the heterogeneity for the different models.

Results

Random-effects model with average effect sizes

In a random-effects model no variables are kept fixed in the calculation of the correlations. If the variables of the studies included in the meta-analysis would have a perfect correlation, no so-called individual specific effects would be found. It would mean that the

relation between the pharmacological or non-pharmacological intervention and the disruption of the reconsolidation process would be total under influence of the variables of the studies included in the meta-analysis. The random-effects model however did show the so-called individual specific effects, which were significant at the alpha .5 level. This means that in a certain amount of studies included in the meta-analysis the just mentioned relationship is also influenced by variables, which were not included in the studies in the meta-analysis. The heterogeneity was 56%; this means that 56% of the studies included in the meta-analysis do not have the so-called individual specific effects; the mentioned relationship in these studies is not influenced by variables, which were not included in the respective studies.

Mixed-effects model with all effect sizes

A mixed-effects model has both random and fixed effects. In fixed effects, variables are added to estimate correlations in a study. This is not necessary for the random effects. For both effects it is possible to determine the so-called individual specific effects. Again, if the relationship between the pharmacological or non-pharmacological intervention and the disruption of the reconsolidation process would be perfect, none of these individual specific effects would be found. This means that this relationship would only be influenced by the variables included in the studies in the meta-analysis. The mixed-effects model however did find some of the so-called individual specific effects. This means that at least a part of the studies included in the meta-analysis have variables influencing the mentioned relationship. These variables are variables not included in the studies in the meta-analysis. These results were significant at the alpha .5 level. The heterogeneity was determined at 77%. This means that 77% of the studies included in the meta-analysis do not have the so-called individual specific effects; the mentioned relationship in these studies is not influenced by variables, which were not included in the respective studies. In the rest of the studies however the mentioned relationship is influenced by variables, which are not included in the studies in the meta-analysis.

Moderation analysis with average effect sizes

The random-effects model and mixed-effects model already showed that in some studies in the meta-analysis the relationship between the pharmacological or non-pharmacological intervention and the disruption of the reconsolidation process is influenced by variables, which were not included in the initial studies. Therefore, a moderation analysis was also conducted. This analysis allows to determine if there indeed is a variable influencing

the mentioned relationship. The effect of a so-called moderator variables can influence the direction and / or strength of the mentioned relationship. The results of the moderation analysis were significant at the alpha .5 level. This means that for a part of the studies included in the meta-analysis a moderator variable was influencing the mentioned relationship. The heterogeneity was 57%. This means that 57% of the studies in the meta-analysis have a moderator variable, which influenced the mentioned relationship between the pharmacological or non-pharmacological intervention and the disruption of the reconsolidation process. The moderation analysis was not used to determine which moderator variables were active in the studies.

Calculation of the fail-safe

As was stated in the introduction, the fail-safe was calculated for this study. The fail-safe was calculated using the Rosenthal approach. Appendix 2 shows the graph for the calculation of the fail-safe. The fail-safe of this study was N = 148. This means that 148 non-significant studies needed to be included that have non-significant results to reach an effect size of zero. This is a high amount of non-significant studies. The main reason for this is that non-publicated studies were not involved in the meta-analysis. Another reason is that not many non-significant studie were included in the literature.

Summary

The results have shown that pharmacological and non-pharmacological interventions can disrupt the reconsolidation process. The different analyses have shown that the greater part of the studies included in the meta-analysis have a correlation between the intervention and the disruption of the reconsolidation process. This correlation holds for all variables involved in a particular study. The results however also showed that a smaller part of the studies included in the meta-analysis are also correlated with another moderator variables. This means that a third variable, which was not included in the initial study, influences the mentioned relationship.

Discussion

This study tried to determine the effects of pharmacological and non-pharmacological interventions on disrupting the reconsolidation process. The first hypothesis of this study was that using pharmacological or non-pharmacological interventions to disrupt the reconsolidation process have a strong effect in terms of diminishing fear. Based on the results of this meta-analysis, this hypothesis is accepted. The results showed that both types of interventions helped diminishing fear; this was shown in different analyses.

The second hypothesis of this study was that pharmacological interventions for disrupting the reconsolidation process have a greater effect size than the non-pharmacological interventions on patients with anxiety and stress related disorders. Based on the results of this meta-analysis, this hypothesis is rejected. The results showed that no significant differences were found between the two types of interventions in terms of effect sizes; this was shown in different analyses.

The first analysis showed no individual specific effects correlating with the pharmacological and non-pharmacological intervention. In 56% of the studies included in the meta-analysis the relationship between pharmacological or non-pharmacological interventions and the disruption of the reconsolidation process is not influenced by variables, which were not included in the studies in the meta-analysis. The results of the meta-analysis show that at least a part of the pharmacological studies involved have these effects in weakening the response to a fearful stimulus. However, non-pharmacological studies, like Schiller et al. (2010) also showed positive effects for weakening fear responses. The results of the non-pharmacological studies provided evidence that non-fearful information can also be provided within the reconsolidation window in order to update old fear memories. As a consequence, in several studies fear responses were no longer expressed. The results of the meta-analysis show that at least a part of the non-pharmacological studies involved also have these effects in weakening the response to a fearful stimulus. Therefore, it can be concluded that both pharmacological and non-pharmacological interventions are able to disrupt the reconsolidation process and weaken fear responses.

The second analysis, with both fixed and random effects, showed individual specific effects correlating with the pharmacological and non-pharmacological interventions. It was shown that 57% of the studies in the meta-analysis has a moderator variable. This is a variable

influencing the mentioned relationship between the pharmacological or non-pharmacological intervention and the disruption of the reconsolidation process. The moderation analysis was not used to determine which moderator variables were active in the studies due to the time frame. The results of the meta-analysis show that at least a part of the pharmacological and non-pharmacological studies involved can disrupt the reconsolidation process and aid in weakening the response to a fearful stimulus.

The third analysis showed that at least a part of the studies in the meta-analysis have a moderator variable influencing the relationship between the independent and dependent variables. In this study, a moderator variable is a third variable, which was not included in the initial studies in the meta-analysis. This variable however does influence the direction and/or strength of the relationship between pharmacological or non-pharmacological interventions and the disruption of the reconsolidation process. This was also confirmed by a heterogeneity of 57%. At least a part of the pharmacological and non-pharmacological interventions in the meta-analysis have a moderator variable involved. The moderator variable influences the effect the intervention has in weakening the fear response. This is true for at least part of the pharmacological and non-pharmacological interventions involved. An indication of a probable moderator variable can be found in the study of Kindt et al. (2009). As was stated before, the results of this study showed that administering propranolol during the reconsolidation process helped weakening the fear response. Since the fear is based on a learned link between CS and US, the expectancies relating to the US remained, despite the fact that the fear response weakened. These fear responses refer to the startle reflex. These results show that administering propranolol only targets startle reflexes and not expectations. In the relationship with expectations, a moderator variable could exert some influence. A later study (Soeter & Kindt, 2015) delivered similar results.

However, based on the study of Kindt et al. (2009) it was also assumed that pharmacological interventions using propranolol would have a greater effect in diminishing fear in patients with anxiety and stress related disorders than non-pharmacological interventions. The results showed that at least a part of the pharmacological and non-pharmacological studies involved in the meta-analysis have a positive effect in weakening the response to a fearful stimulus. These results however did not indicate better results with either pharmacological or non-pharmacological interventions. Both types of interventions can indeed disrupt the reconsolidation process.

This study however is prone to publication bias. A large number of non-significant studies would have to be included to have an effect of zero (Rosenthal, 1979, in: Becker, 2005). For any conducted study, a number of other studies will not be published. The assumption in calculating the fail-safe is that these additional studies have an effect size of zero. With other words, these studies have insignificant results. The fail-safe estimates the number of additional studies needed to turn the effect size of the total studies included in this meta-analysis to zero. Since the fail-safe number for this study was high, the publication bias is also high.

Emotional memories

Reconsolidation can be used to change emotional memories. The meta-analysis however did not state in which way the emotional memories were changed. It can be assumed that emotional memories related to a more traumatic event might show different results due to reconsolidation than emotional memories related to less traumatic events. Future research could focus on averaging the level of traumatic event related to the emotional memories.

Implications for treatment

It was shown that both pharmacological and non-pharmacological interventions can change emotional memories. One of the assumptions was that one type of treatment would show better results. However, both types of interventions showed the ability to change emotional memories. At one hand, this can be considered positive for the treatment of people with anxiety en stress related disorders. If one kind of treatment does not deliver the expected results, the other type could be used. But also one type of treatment can be used as an addition to the applied intervention. However, further research is still needed in which cases this is possible.

Limitations

This study showed limitations in three ways. One, it was limited due to the publication bias, since no unpublished literature was used. Second, the level of traumatic event related to the emotional memories was not included. Finally, time was also an issue. Due to a limited time frame, it can be assumed that not all available studies, which met the inclusion criteria, were included in the meta-analysis.

Future research

Still, the results contribute to the discussion of the effects of different interventions for interrupting the reconsolidation process in diminishing fear in people with anxiety or stress related disorders. Further research is needed to determine the total effects of both types of interventions. Further research can aim at specific results for the two types of interventions, but can also aim at identifying the specific effect sizes for either type of intervention. The study has contributed to the existing literature and research on the matter because it has shown that applying either type of intervention in the reconsolidation process is not a lineair process. It has also contributed to the reigning discussion about which type of intervention provides the best results.

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Figures

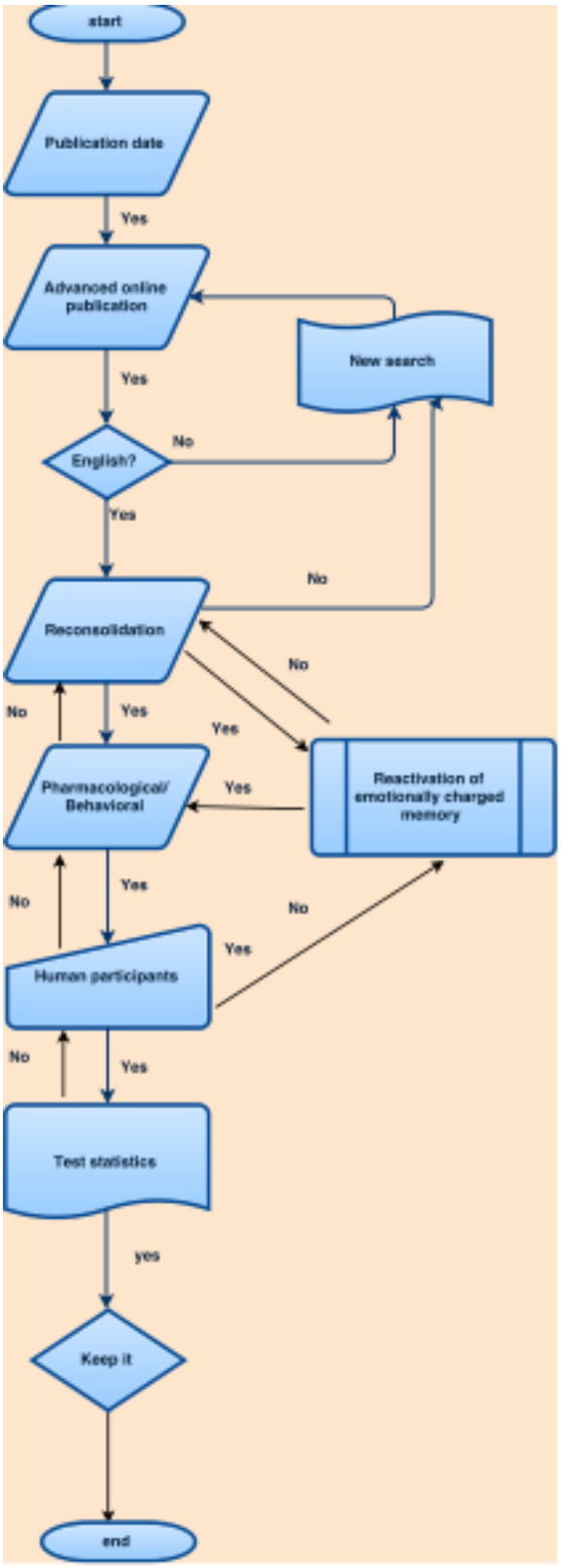

Figure 1. Model with criteria for article selection

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## Fail-safe N Calculation Using the Rosenthal Approach
## Observed Significance Level: 0.0004
## Target Significance Level:   0.05
## Fail-safe N: 148
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Figure 2. Calculation of fail-safe using the Rosenthal approach in R