New learning following reactivation in the human brain: Targeting emotional memories through rapid serial visual presentation

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ABSTRACT

Once reactivated, previously consolidated memories destabilize and have to be reconsolidated to persist, a process that might be altered non-invasively by interfering learning immediately after reactivation. Here, we investigated the influence of interference on brain correlates of reactivated episodic memories for emotional and neutral scenes using event-related potentials (ERPs). To selectively target emotional memories we applied a new reactivation method: rapid serial visual presentation (RSVP). RSVP leads to enhanced implicit processing (pop out) of the most salient memories making them vulnerable to disruption. In line, interference after reactivation of previously encoded pictures disrupted recollection particularly for emotional events. Furthermore, memory impairments were reflected in a reduced centro-parietal ERP old/new difference during retrieval of emotional pictures. These results provide 0neural evidence that emotional episodic memories in humans can be selectively altered through 0behavioral interference after reactivation, a finding with further clinical implications for the treatment of anxiety disorders.

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1. Introduction

Changing unpleasant or even traumatic memories is one of the major challenges for clinical interventions (Parsons & Ressler, 2013). It is a well-established finding that the formation of emotional long-term memories is mediated by the adrenergic system and depends on the interaction between amygdala and hippocampus (McGaugh, 2000). Following retrieval consolidated memories return to an unstable state and have to be stabilized again into a persisting memory, a process that is known as memory reconsolidation (Nader, Schafe, & LeDoux, 2000). Recent animal and human research has successfully targeted the modification of conditioned fear memories through blockade of reconsolidation after reactivation of these memories by pharmacological agents, such as beta-adrenergic receptor blockers (Nader & Hardt, 2009; Nader et al., 2000). To date, psychophysiological and emerging behavioral evidence exists for successful blockade of reconsolidation in humans using pharmacological or behavioral interventions (Chan & LaPaglia, 2013; Schiller et al., 2010; for review see Agren, 2014). For instance, it has been shown that new learning after reactivation of previously learned material may impair (Wichert, Wolf, & Schwabe, 2011) or update (Hupbach, Gomez, Hardt, & Nadel, 2007) memory. Despite promising behavioral evidence only few brain imaging studies (Agren et al., 2012; for review see Schwabe, Nader, & Pruessner, 2014) investigated human brain function underlying altered memory representations following reconsolidation blockade in humans. Agren et al. (2012) found that behavioral disruption of fear reconsolidation significantly decreased memory trace activity in the amygdala. Using pharmacological reconsolidation blockade, Schwabe, Nader, Wolf, Beaudry, and Pruessner (2012) found that impairments in memory for emotional materials were associated with altered amygdala and hippocampus activation.

In the present study we used event-related potentials (ERPs) to investigate the brain dynamics underlying episodic emotional memories. ERPs provide non-invasive measures of neural activity with high time resolution (ms range) and are thus well suited to examine the neural networks underlying human memory (Voss & Paller, 2008). In recognition memory tasks it is a key finding that ERPs during the retrieval of previously encoded "old" items evoke more positive going waveforms than correctly classified "new" items (Rugg et al., 1998). This so-called ERP old/new effect is most prominent over centro-parietal brain sites, starting at about 500 ms post-stimulus, and has been associated with hippocampus-dependent explicit recollection (Düzel, Vargha-Khadem, Heinze, & Mishkin, 2001). Numerous studies have found that the late ERP old/new effect is specifically enhanced for emotionally arousing compared to neutral stimuli (Weymar & Hamm, 2013), an effect that can be abolished by pre-encoding beta-adrenergic blockade (Weymar et al., 2010). The beta-adrenergic system also

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mediates the reconsolidation of conditioned fear memory in humans (Kindt, Soeter, & Vervliet, 2009).

Here, we tested whether encoding of new information after reactivation of previously encoded memories interferes with the reconsolidation of reactivated emotional and neutral episodic memories and whether this interference can be traced in the neural signature of episodic memory. We applied a new method for memory reactivation – rapid serial visual presentation (RSVP). During this task all 90 previously encoded pictures were presented in a rapid stream so that the entire reactivation lasted only for 30 s (Versace, Bradley, & Lang, 2010). Based on previous research four experimental groups were included in the design (see Fig. 1). In two groups old memories were reactivated using the 30 s RSVP after one day and reconsolidation of these old memories were interrupted after 10 min by an interfering task (encoding of new emotional and neutral scenes) in one group but not in the other. Two groups without the reactivation manipulation were added as control groups. One of these groups just received the interference task on day two to assess the unique influence of the interference task.

We expected that new learning, compared to no learning, would impact reconsolidation of previously reactivated pictures. Because pictures were reactivated through RSVP – favoring the processing of salient stimuli – we predicted that particularly emotional memories would be affected by the interference task resulting in impaired recognition memory performance and smaller centro-parietal old/new difference in the ERPs.

2. Material and methods

2.1. Participants

Eighty-eight individuals participated in the study. Exclusion criteria were checked in a standardized telephone interview and included current or lifetime diagnosis of mental disorders, current medical conditions and medication intake during study participation. Participants who missed the second (after 1 day) and/or third session (after 7 days) were excluded and were not tested further ($n = 8$). The final sample included 80 healthy male participants (mean age: 24.1 years, range: 19–31, 4 left handed). All participants had normal or corrected-to-normal vision. Participants provided informed written consent for the protocol approved by the Review Board of the University of Greifswald in accordance with the provisions of the World Medical Association Declaration of Helsinki and received financial compensation for participation.

2.2. Stimulus materials and procedure

Stimuli consisted of 270 pictures (90 unpleasant, 90 neutral and 90 pleasant pictures) taken from the International Affective Picture Series (IAPS) (Lang, Bradley, & Cuthbert, 2008) and the Emotional Picture Set (EmoPicS) (Wessa et al., 2010). Three stimulus sets, each consisting of 90 pictures (30 unpleasant, 30 neutral and 30 pleasant pictures) were carefully matched according to their normative valence and arousal ratings (see IAPS and EmoPicS norms for males; Set 1: mean valence = 3.1, 5.1 and 7.1, mean arousal = 5.7, 3.3 and 6.0; Set 2: mean valence = 3.0, 5.1 and 7.1, mean arousal = 5.8, 3.2 and 5.8; Set 3: mean valence = 2.9, 5.2 and 7.0, mean arousal = 5.8, 3.2 and 5.9 for unpleasant, neutral and pleasant pictures respectively). The three sets were also matched for semantic categories (e.g. attack, mutilation, neutral people, objects, adventure, and erotic couples).

Forty-two additional pictures were added before (7 unpleasant, 7 neutral, 7 pleasant) and after (7 unpleasant, 7 neutral, 7 pleasant) the encoding picture presentation (day one) to avoid serial position effects on subsequent memory performance. These pictures were not included in the analyses. The three picture sets were counterbalanced across participants and the four experimental groups to serve either as encoding picture set, interference learning set or as a new picture set during recognition memory testing.

Individual hedonic valence and arousal ratings for all pictures were obtained to control for group differences in our sample (Bradley & Lang, 1994). As expected, unpleasant pictures were rated as more unpleasant (mean valence: 2.7) than neutral (mean valence: 5.5; $F_{(1,78)} = 1010.33$, $p < .001$) and pleasant (mean valence: 6.8, $F_{(1,78)} = 1366.67$, $p < .001$) pictures. Pleasant pictures were more pleasant than neutral pictures ($F_{(1,78)} = 363.69$, $p < .001$). Additionally, emotional pictures (unpleasant (mean arousal: 5.6) and pleasant (mean arousal: 4.5)) were rated as more arousing than neutral pictures (mean arousal: 2.1; $F_{(1,78)} = 746.47$, $p < .001$). Hedonic valence ($F_{(6,150)} < 1$, $p = .81$) and arousal ratings ($F_{(6,150)} < 1$, $p = .91$) of the pictures in the three sets did not differ between the four experimental groups. During the encoding session, 90 pictures as well as the 42 buffer pictures were presented on a 20-inch computer screen for 3000 ms with a random inter-trial interval (ITI) of 2000, 2500 or 3000 ms. A 500 ms fixation cross preceded every picture onset to ensure that participants fixated the center of the screen. The pictures were presented in pseudorandom order for each participant with the restriction that no picture from the same valence category was presented on two consecutive trials.

On the first day of the experiment, all participants encoded ninety pictures (30 unpleasant, 30 pleasant, 30 neutral) and were randomly assigned to one of four experimental groups (Fig. 1). Participants were instructed to attentively watch the pictures. No mention of a memory test was made (incidental encoding).

Twenty-four hours later, participants in the *Reactivation group* ($n = 20$) returned to the lab for reactivation of the previously seen pictures using RSVP (3 Hz). The rationale for this approach was as follows: Because memory for emotional scenes is exceptional even
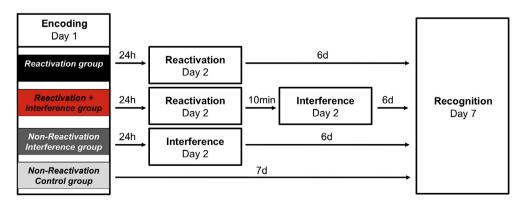

Fig. 1. Experimental design. The four experimental groups (Reactivation, Reactivation + interference, Non-Reactivation Interference, Non-Reactivation Control) and time intervals between the experimental sessions (Encoding, Reactivation, Interference learning task and Recognition).