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Representational similarity analysis offers a preview of the noradrenergic modulation of long-term fear memory at the time of encoding

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Summary Neuroimaging research on emotional memory has greatly advanced our understanding of the pathogenesis of anxiety disorders. While the behavioral expression of fear at the time of encoding does not predict whether an aversive experience will evolve into long-term fear memory, the application of multi-voxel pattern analysis (MVPA) for the analysis of BOLD-MRI data has recently provided a unique marker for memory formation. Here, we aimed to further investigate the utility of this marker by modulating the strength of fear memory with an α2-adrenoceptor antagonist (yohimbine HCl). Fifty-two healthy participants were randomly assigned to two conditions — either receiving 20 mg yohimbine or a placebo pill (double-blind) — prior to differential fear conditioning and MRI-scanning. We examined the strength of fear associations during acquisition and retention of fear (48 h later) by assessing the similarity of BOLD-MRI patterns and pupil dilation responses. Additionally, participants returned for a follow-up test outside the scanner (2—4 weeks), during which we assessed fear-potentiated startle responses. Replicating our previous findings, neural pattern similarity reflected the development of fear associations over time, and unlike average activation or pupil dilation, predicted the later expression of fear memory (pupil dilation 48 h later). While no effect of yohimbine was observed on markers of autonomic arousal, including salivary α-amylase (sAA), we obtained indirect evidence for the noradrenergic enhancement of fear memory consolidation: sAA levels showed a strong increase prior to fMRI scanning, irrespective of whether participants had received yohimbine, and this increase correlated with the subsequent

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expression of fear (48 h later). Remarkably, this noradrenergic enhancement of fear was associated with changes in neural response patterns at the time of learning. These findings provide further evidence that representational similarity analysis is a sensitive tool for studying (enhanced) memory formation.

1. Introduction

Whereas much of what we learn will be forgotten with the passage of time, emotional memory appears to be particularly resilient to forgetting (LaBar and Cabeza, 2006; McGaugh, 2000; McGaugh and Roozendaal, 2002; Pape and Paré, 2010). Long-lasting memory for emotional experiences is in principle adaptive, but can become dysfunctional as in the case of anxiety disorders.

The quintessential model for studying fear learning and memory is Pavlovian fear conditioning, describing how a previously neutral event (Conditioned Stimulus, CS) elicits fear responses after it has become associated with an aversive event (Unconditioned Stimulus, UCS). The traditional fear-conditioning paradigm was originally designed to explore normal processes of fear learning and memory. Given that anxiety disorders are characterized by the persistence of fear, and by generalization of fear to other stimuli and contexts in the absence of actual danger, abnormal fear memory as such cannot be defined at the time of learning. In laboratory settings, however, abnormal fear memory can become apparent at later retention tests. A key question is whether the processes that lie at the root of the development of abnormal fears are already active during the initial phase of associative fear learning, or whether they are predominantly active during the post-encoding consolidation phase.

To mimic abnormal processes of fear learning and memory, the noradrenergic system can be stimulated during or immediately after fear conditioning, either directly through the central administration of noradrenaline (LaLumiere et al., 2003), or indirectly through the administration of the α2-adrenoceptor antagonist yohimbine HCl (Gazarini et al., 2013, 2014; Soeter and Kindt, 2011, 2012). By blocking the α2-adrenergic autoreceptor, yohimbine interrupts the negative feedback control of noradrenaline release, thereby increasing noradrenergic activity (Hedler et al., 1981; Langer, 1974; Wemer et al., 1979). This experimental model has been shown to strengthen fear memory, characterized by the persistence and overgeneralization of fear (Gazarini et al., 2013, 2014; Soeter and Kindt, 2011, 2012). Interestingly, the effect of yohimbine administration prior to fear learning was not yet expressed at the time of learning (i.e., in more differential startle potentiation or elevated skin conductance; Soeter and Kindt, 2011, 2012), suggesting that post-learning processes accounted for this enhancement. Indeed, ample evidence supports the role of noradrenaline in synaptic changes, including long-term potentiation (LTP), underlying the stabilization of a memory trace after its acquisition (Cahill et al., 1994; Cahill and Alkire, 2003; Hurlemann et al., 2005; Southwick et al., 2002; Strange and Dolan, 2004).

A crucial question is, however, whether the most commonly used physiological measures in fear-conditioning paradigms are in this case reliable indicators of the formation of fear memory. An inherent restriction of all memory research, including fear conditioning, is that one cannot assess what is stored in memory until a memory is expressed. Yet, behavior during learning (e.g., freezing in rats, physiological responding in humans) is not necessarily predictive of long-term memory, as much of what we learn will be either lost over time or will not be consolidated in the first place. In order to establish whether the memory enhancing properties of noradrenaline are already at play during a learning experience, a reliable (neural) signature for the formation of fear memory is required. Ideally, such a marker would indicate during learning whether, and how well, information will subsequently be consolidated.

In a recent functional Magnetic Resonance Imaging (fMRI) study, we applied representational similarity analysis (Kriegeskorte et al., 2008; Visser et al., 2011) to show that changes in neural response patterns at the time of encoding were predictive of the long-term physiological (i.e., pupil dilation) expression of fear memory (Visser et al., 2013), while the physiological expression during fear learning did not predict the later expression of fear. Specifically, we showed that response patterns evoked by two unrelated stimuli became alike as a result of their association with an aversive outcome (between-stimulus pattern similarity). The degree to which these patterns became similar predicted differential pupil responses 2—6 weeks later. This suggests that part of the consolidation process, or the selection of information for subsequent consolidation, already occurs during learning, but cannot be observed in indices of peripheral nervous system activity. The question is whether noradrenergic *enhancement* of fear associations can also be observed in neural patterns at the time of learning, indicating that the transition from normal fear to excessive fear may start instantaneously.

Here, we further investigate whether changes in neural response patterns at the time of learning are (1) a marker for memory formation and (2) related to changes in noradrenergic activation. In previous studies, noradrenergic enhancement resulted in a stronger fear memory, expressed as increased fear responses, slower extinction of learned fear, stronger reinstatement and reacquisition of a successfully extinguished fear and (over)generalization of fear to other stimuli and contexts (Gazarini et al., 2013, 2014; Soeter and Kindt, 2011, 2012). In the current experiment, consisting of three sessions (separated by 48 h and 2—4 weeks, respectively), we incorporated similar tests of long-term fear memory, including extinction, reinstatement and generalization of fear (Session 2) and renewal and reacquisition of fear (Session 3). We measured BOLD activation, pupil dilation (Sessions 1 and 2), and fear-potentiated startle responses (Session 3), in order to assess at what point in time