

# Neurobiological Correlates of Emotion Regulation

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“Worry is like a rocking chair:  
it gives you something to do  
but never gets you anywhere.”

*Erma Bombeck*



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# Abstract

Psychological health is a result of the effective interplay between explicit and implicit attempts to regulate ones' emotions (Koole & Rothermund, 2011). Emotion regulation refers to processes that influence the intensity, the duration and the type of emotion experienced (Gross & Thompson, 2007). While explicit emotion regulation comprises effortful mental processes, implicit emotion regulation refers to processes that require no monitoring and terminate automatically (Gyurak, Gross, & Etkin, 2011).

In the present thesis, explicit and implicit strategies to regulate emotions were investigated. In Study 1, a well-established paradigm (Gross & Levenson, 1993) was adapted to examine the up- and down-regulation of positive and negative emotions using two different explicit emotion regulation strategies. To infer on the neurobiological correlates, blood oxygen level dependent (BOLD) brain activity was recorded using functional magnetic resonance tomography. Furthermore, as a trait marker for the individual ability to regulate emotions, heart rate variability (HRV) was acquired during rest. In Study 2, implicit emotion regulation was examined. Therefore, a well-established fear extinction paradigm was compared to a novel approach based on the integration of new information during reconsolidation (Schiller et al., 2010). Autonomic arousal was measured via the skin conductance response during fear acquisition, fear extinction and after fear reinstatement. In Study 3, two dysfunctional emotion regulation strategies —worrying and rumination— were investigated. Excessive worrying and rumination are pathogenic characteristics of psychological disorders. Behavioral, autonomic and BOLD activity was recorded during worried and ruminative thinking as well as during neutral thinking.

The results showed that explicit emotion regulation was associated with modulated BOLD activity in the amygdala according to the regulation direction independent of the applied strategy and the valence of the emotion. In addition, increased dorsolateral prefrontal cortex (dlPFC) activity was observed during regulation compared to passively viewing emotional pictures. The findings are in line with previous research

(Eippert et al., 2007; Kim & Hamann, 2007; Ochsner et al., 2004) and support the key role of the dlPFC during the explicit regulation of emotions. Similarly, implicit emotion regulation was associated with a decreased autonomic fear response, which was sustained after fear extinction during reconsolidation. The findings underscore the notion, that this novel technique might alter the initial fear memory resulting in a permanently diminished fear response (Nader, Schafe, & LeDoux, 2000; Schiller et al., 2010). Dysfunctional emotion regulation was associated with increased autonomic activity and fear potentiated startle (during worry) as well as increased BOLD activity in the insula (during worry and rumination) and increased BOLD activity in the amygdala (during rumination). In addition, neural activity in brain areas associated with the default mode network was observed. These findings stress the preserved negative emotional activity and the self-referential nature of the examined dysfunctional strategies. The results of all three studies are integrated into a neurobiological model of emotion regulation focusing on the interplay between subcortical and prefrontal brain areas.

# Zusammenfassung

Psychologische Gesundheit ergibt sich aus dem effektiven Zusammenspiel von expliziten und impliziten Bemühungen die eigenen Emotionen zu regulieren (Koole & Rothermund, 2011). Emotionsregulation umfasst Prozesse, welche die Intensität, die Dauer oder die Art der emotionalen Erfahrungen beeinflussen (Gross & Thompson, 2007). Dabei bezieht sich die explizite Emotionsregulation auf aufwendige Prozesse und die implizite Emotionsregulation auf Prozesse, deren Umsetzung keiner Überwachung bedarf und die automatisch bis zur ihrem Abschluss ablaufen (Gyurak et al., 2011).

In der vorliegenden Arbeit wurden verschiedene explizite und implizite Strategien der Emotionsregulation erforscht. In Studie 1 wurde ein gut etabliertes Paradigma (Gross & Levenson, 1993) angepasst, um die Verstärkung und die Verringerung positiver und negativer Emotionen mit zwei verschiedenen expliziten Emotionsregulationsstrategien zu untersuchen. Um Rückschlüsse auf die neurobiologischen Korrelate zu ziehen, wurden die Veränderungen des Blutsauerstoffgehalts (BOLD) im Gehirn mit Hilfe der funktionellen Magnet-resonanztomographie gemessen. Außerdem wurde die Herzratenvariabilität (HRV) im Ruhezustand als Indikator einer überdauernden individuellen Emotionsregulationsfähigkeit erfasst. In Studie 2 wurde die implizite Emotionsregulation untersucht. Dazu wurde ein Standardparadigma zur Furchtextinktion mit einem neuartigen Ansatz verglichen, welcher auf der Integration neuer Informationen während der Rekonsolidierung beruht. Die autonome Erregung wurde anhand der Hautleitfähigkeit während der Furchtakquisition, der Furchtextinktion und nach dem Wiedereinsetzen der Furcht gemessen. In Studie 3 wurden zwei dysfunktionale Emotionsregulationsstrategien – ‘Sich Sorgen’ und ‘Grübeln’ – untersucht. Sowohl exzessives sich Sorgen als auch Grübeln sind pathogenetische Merkmale psychischer Störungen. Autonome, behaviorale und neurobiologische Veränderungen wurden während des Sorgens, des Grübelns und des Nachdenkens über neutrale Themen gemessen.

Die Ergebnisse zeigten, dass die explizite Emotionsregulation mit modulierter

BOLD-Aktivität in der Amygdala entsprechend der vorgegebenen Regulationsrichtung assoziiert war. Dieser Effekt war unabhängig von der verwendeten Emotionsregulationsstrategie und der Valenz der Emotion. Außerdem wurde eine erhöhte Aktivität im dorsolateralen präfrontalen Kortex (dlPFC) während der Regulation im Vergleich zum passiven Betrachten der emotionalen Bilder beobachtet. Diese Ergebnisse decken sich mit anderen Befunden (Eippert et al., 2007; Kim & Hamann, 2007; Ochsner et al., 2004) und unterstreichen die zentrale Rolle des dlPFCs für die explizite Emotionsregulation. In ähnlicher Weise war die implizite Emotionsregulation mit einer verringerten autonomen Reaktion assoziiert, wobei diese anhielt, wenn die Furchtextinktion während der Rekonsolidierung erfolgte. Diese Befunde unterstreichen die Ansicht, dass diese neuartige Technik das ursprüngliche Furchtgedächtnis verändert und somit zu einer dauerhaften Reduktion der Furchtreaktion führt (Nader, Schafe, & LeDoux, 2000; Schiller et al., 2010). Dysfunktionale Emotionsregulation war mit erhöhter autonomer Aktivität und einer Potenzierung der Schreckreaktionen (während des Sorgens), sowie mit erhöhter BOLD Aktivität in der Insel (während des Sorgens und des Grübelns) und in der Amygdala (während des Grübelns) assoziiert. Außerdem wurde neuronale Aktivität in Hirnregionen des ‘default mode networks’ beobachtet. Diese Befunde unterstreichen die Aufrechterhaltung der negativen Emotionalität, sowie die selbstbezogene Natur der beiden untersuchten dysfunktionalen Strategien.

Die Ergebnisse aller drei Studien werden diskutiert und in ein neurobiologisches Model der Emotionsregulation integriert. Der Fokus liegt dabei auf der Interaktion von subkorticalen und prefrontalen Hirnregionen.

# 1 An introduction to emotion regulation

Imagine an employee being screamed at for a minor mistake by a choleric employer. In response, the heartbeat might increase, muscles might tense up and maybe even her or his fists might clench. Thoughts might become vicious and she or he may feel the urge to scream back at the employer. This example describes that emotions evolve in response to motivationally relevant stimuli and initiate physiological, subjective, motor and cognitive changes that prepare the body for action (Frijda, 1986; Lang, Bradley, & Cuthbert, 1997). Hence, they have the power to interrupt ongoing behavior and mental processes and influence how we think, feel and behave (Gross, 2014).

However, it is possible to withstand these powerful urges and respond flexibly in order to maintain social relationships and pursue long-term goals (John & Gross, 2004; Tamir & Ford, 2011). We do it every day (Gross, Richards, & John, 2006), for example, one might reappraise the upcoming anger in order to keep her or his position until finding another job. In fact, the inability to regulate one's emotions is a major characteristic in psychological (Gross & Levenson, 1997) and physical disorders (Sapolsky, 2007). For example, an individual with depression might respond by ruminating about the mistake and one's own failure. Whereas an individual with generalized anxiety disorder might respond with exuberant worries about being fired. Both individuals, however, might not fully process the anger and as a result they might not be able to confidently search for a new job.

Historically, the question of how to regulate emotions has been highly entangled with the question about the nature of emotions and dates back to ancient philosophers (e.g., Aristotele, Seneca). However, in the past two decades, emotion regulation has been established as a distinct research field (e.g., Gross, 2015). According to a widely accepted definition in the field, emotion regulation refers to goal-directed processes that influence the intensity, the duration and the type of emotion experienced

(Gross & Thompson, 2007). This, however, can be achieved in numerous different ways. One approach to classify and integrate these attempts is the dual-process framework, which distinguishes explicit and implicit attempts to alter emotional responses (Gyurak, Gross, & Etkin, 2011). Implicit processes require no monitoring, insight or awareness; instead, they are evoked automatically by the stimulus itself and they are terminated automatically (Gyurak et al., 2011). In contrast, explicit processes require the effortful application of emotion regulation strategies (Gyurak et al., 2011). Adaptive emotion regulation is mostly based on the interplay of implicit and explicit processes (Gyurak et al., 2011).

On a neurobiological level, both types of emotion regulation are characterized by the interaction of emotion-generating and -controlling systems. Emotion generation is primarily reflected by neurobiological activity in subcortical circuits (Damasio et al., 2000). Particularly, the amygdala with its highly selective sensitivity to motivationally-relevant cues plays a crucial role (Hamm & Weike, 2005; Phelps & LeDoux, 2005; LeDoux, 1996). Upon the detection of these cues in the environment, the amygdala rapidly initiates and modulates an emotional response in the autonomic, cognitive, perceptual, memory and motor systems (Hamm & Weike, 2005). Although the amygdala has long been discussed as the key region involved in fear acquisition, storage and expression (LeDoux, 1996), it has also been found responsible for the arousing properties of pleasant stimuli (Hamann, Ely, Grafton, & Kilts, 1999). In studies of explicit and implicit emotion regulation, amygdala activity is typically recorded as an index of an emotional response: Increased activity is associated with increased emotional intensity or fear acquisition whereas decreased amygdala activity is associated with successfully reduced emotional arousal or fear extinction (e.g., LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998; Ochsner, Bunge, Gross, & Gabrieli, 2002). In addition, the insular cortex plays an important role in the generation of emotions. Since all visceral afferents converge here, the activity in the insula cortex is thought to reflect self-induced or internally generated emotions and the subjective emotional experience of emotions (Craig, 2003; Critchley, Wiens, Rotshein, Öhman, & Raymond, 2004; Phan, Wager, Taylor, & Liberzon, 2002).

To conclude, the highly automatic bottom-up processes characterizing the emotion-generating system are mainly driven by the amygdala and the insula. The amygdala is relevant for the rapid detection of biologically relevant stimuli and the rapid initiation of an autonomic response. The insula is relevant for the perception of the initiated changes in the body (interoception) and the feeling state. During emotion

regulation, higher order control processes initiated by cortical brain regions modulate these processes.

The prefrontal cortex, especially, is considered to modulate emotional responses. Meta-analyses on the cognitive control of emotions have consistently shown an activation of the dorsolateral prefrontal cortex (dlPFC; Kohn et al., 2014; Buhle et al., 2013), which is traditionally associated with cognitive control and working memory (Gazzangia, Ivry, & Mangun, 2008). The dlPFC seems to be important for the representation of goal states (Davidson, Jackson, & Kalin, 2000) and for the reappraisal of the relationship between internal and external events (Ochsner & Gross, 2004). It has been shown that the higher the success of emotion regulation, the stronger the negative connectivity between the dlPFC and the amygdala (Lee, Heller, van Reekum, Nelson, & Davidson, 2012). However, the control of the dlPFC on the amygdala seems to be exerted not directly but indirectly via the ventromedial PFC (vmPFC). Firstly, the dlPFC has relatively sparse direct anatomical connections to the amygdala compared to the vmPFC (Ghashghaei, Hilgetag, & Barbas, 2007), and secondly, the vmPFC is similarly activated during emotion regulation (Urry et al., 2006). In the same way, research based on fear extinction highlights the interaction between the amygdala and the vmPFC (Quirk & Mueller, 2008). The vmPFC seems to be a region where inputs from different brain areas are integrated to modulate the emotional response: evaluations of the arousing properties by the amygdala, the knowledge from prior experience with the stimulus by medial temporal areas, the information about the current motivational state by brainstem areas, and the information about current behavioral goals by the PFC (Ochsner, Silvers, & Buhle, 2012; Roy, Shohamy, & Wager, 2012).

To illustrate how emotion generation and regulation are intertwined on a neurobiological level, imagine again the situation of the employee and the choleric employer. The motivationally relevant stimulation will activate the amygdala, which rapidly initiates an emotional response (e.g., increase in blood pressure and muscle tension, tendency to shout back) associated with a feeling of anger probably mediated by the insular cortex. Prefrontal networks are then recruited to modulate this response, for instance, the dlPFC might bring the goal to keep one's job to the forefront of one's attention and select an appropriate reappraisal strategy for the situation, as a specific example, thinking about one's financial situation for the month. The vmPFC will assist by bringing up what reappraisal worked last time and constantly monitoring how this reappraisal is implemented and how it affects the emotional response. As a

result the intensity of the emotional response will decrease and the action tendency will be inhibited. Of course, these direct translations are oversimplifying the actual, much more complex processes that rely on highly interconnected brain networks for their implementation.

## 2 Explicit emotion regulation

According to Richards & Gross (2000), explicit emotion regulation can be defined as “the evocation of thoughts or behaviors that influence which emotions people have, when people have them, and how people experience or express these emotions” (p. 411). In fact, explicit emotion regulation comprises processes that “require controlled effort for initiation, demand some level of monitoring during implementation, and are associated with some level of insight and awareness” (Gyurak et al., 2011, p. 401). Following the widely accepted model of emotion regulation by Gross (1998, see Figure 1), emotion regulation strategies are categorized by the time point at which they affect the emotion-generation process: Strategies are classified as antecedent-focused when they influence the emotion-generating appraisal processes. Strategies are classified as response-focused when applied once appraisal processes have been terminated, and when emotions have become distinct response tendencies. Response-focused strategies can target all components of the emotional response, for example the behavioral expression, the verbal expression, or the physiological response (Gross & Munoz, 1995). To date, the most intensively studied response-focused strategy is suppression, which concentrates on one dimension of the emotional response: hiding the facial expression of the emotion (Gross, 1998). Antecedent-focused strategies are further categorized by their way of modulating the appraisal cycle (Gross, 1998). The most commonly studied form is reappraisal, a cognitive-linguistic strategy (Goldin, McRae, Ramel, & Gross, 2008), influencing the emotion generation before emotional reactions have fully unfolded by changing the cognitive representation of events (Gross & Thompson, 2007). Reappraisal is considered to be one of the most flexible and effective means of reducing the negative impact of an aversive event (Ochsner et al., 2002).

Emotion regulation requires not only the ability to select, implement, monitor and terminate an adequate strategy, but most crucially, that the execution of these processes is fast (Gross, 1998). Heart rate variability (HRV) indicates velocity and flexibility of adaptation to changes in the environment (Task Force Guidelines, 1996)

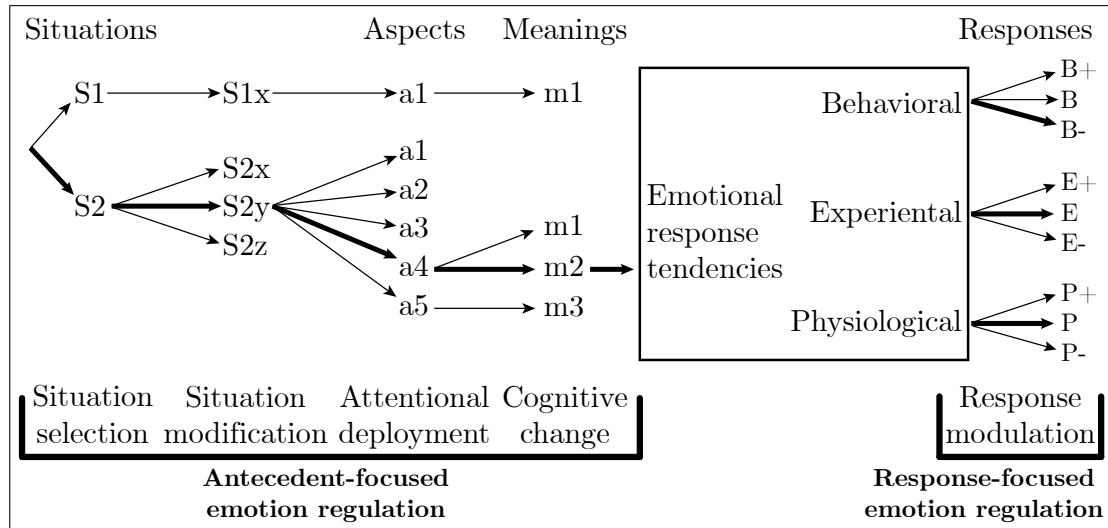


Figure 1: A process model of emotion regulation. Adapted from The Emerging Field of Emotion Regulation: An Integrative Review (Gross, 1998).

and is interpreted as indexing vagal tone to the heart (Porges, 1991). Moreover, high HRV has been linked to cognitive flexibility (Thayer, Hansen, Saus-Rose, & Johnsen, 2009) and better subjective well-being (Geisler, Vennewald, Kubiak, & Weber, 2010). Accordingly, HRV has been related to prefrontal activation, thus providing a direct link to emotion regulation.<sup>1</sup>

## Study 1: Reappraisal and response modulation

To examine the neurobiological correlates of two explicit types of emotion regulation, Steinfurth, Wendt, and Hamm (2013; see Manuscript 1, Appendix A) and Steinfurth, Wendt, Geisler, Hamm, Thayer, and Koenig (in prep.; see Manuscript 2, Appendix A) extended a frequently applied picture viewing paradigm (Eippert et al., 2007; Gross & Levenson, 1993; Ochsner et al., 2002) to a full factorial design including the task of regulating positive emotions as well as counter-hedonic regulation directions, for example to increase negative emotions and decrease positive emotions. Functional magnetic resonance imaging (fMRI) was used to record the blood oxygen level dependent (BOLD) activity during the emotion regulation task. Furthermore, these strategies were related to HRV, an index of vagal control of the heart, that has

<sup>1</sup>Particularly, inhibitory control of the PFC seems to be responsible for this fast parasympathetic modulation of the heart, directly via the nucleus of the solitary tract (NTS) and indirectly via the amygdala (Thayer & Brosschot, 2005; Thayer & Lane, 2000).

been linked to cognitive functioning and prefrontal control. Therefore, resting HRV was recorded prior to the emotion regulation task. During the task pleasant, neutral, and unpleasant pictures from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2008) were presented and participants were instructed to increase, maintain or decrease their initial emotional response using reappraisal and response modulation. During reappraisal, participants were trained (1) to increase or (2) to decrease their emotions. In the first case participants were instructed to imagine being either personally involved in the scene or that the scene would involve persons to whom they have a close relationship. In the second case participants were instructed to increase the distance by imagining the picture as a simulation or by imagining being a casual bystander. For the use of response modulation, participants were trained either (1) to intensify or (2) to reduce the bodily responses elicited by the depicted scenes (e.g., respiration, body tension, and facial expression) to the extent that a possible spectator should either (1) recognize the experienced emotion or (2) not.

The results showed, that viewing of emotional pictures was associated with increased BOLD activity in the amygdala compared to neutral images (Steinfurth et al., 2013). During the subsequent emotion regulation task, BOLD activity in the amygdala decreased during down-regulation and increased during up-regulation. This bi-directional modulation was independent of the regulation strategy and the valence of the emotion. Verbal report measures supported these findings. Furthermore, increased BOLD activity was observed in the dlPFC during both the up- and down-regulation independent of the strategy that was used (Steinfurth et al., 2013). In line with previous research (Eippert et al., 2007; Ochsner et al., 2004), these results indicate that prefrontal cortical control processes were responsible for the successful modulation of amygdala activity extending previous findings to positive emotions and to counter-hedonic regulation directions (Eippert et al., 2007; Kim & Hamann, 2007; Ochsner et al., 2004).

Additionally, participants' ability to regulate negative emotions was effected by their trait like vagal tone (Steinfurth et al., in prep.). For participants with high high-frequency HRV (HF-HRV), BOLD activity in the amygdala was increased and decreased according to the regulation direction when using reappraisal. For participants with low HF-HRV this bidirectional modulation was observed when using response modulation. Similarly, dorsomedial PFC activity was increased in participants with high HF-HRV when using reappraisal and in participants with low

HF-HRV when using response modulation.

These results indicate that individuals might differ in their regulatory success using different regulation strategies depending on their vagal tone. In particular, individuals who generally adapt quicker to environmental demands (high HF-HRV) may benefit even more from a more adaptive explicit emotion regulation strategy. Indeed, previous research showed, that the positive relationship between HRV and subjective well-being is modulated by the habitual use of reappraisal (Geisler et al., 2010).

### 3 Implicit emotion regulation

In the long run, the habitual use of an explicit emotion regulation strategy might increase its efficiency by decreasing the amount of explicit, effortful processes involved (Gyurak et al., 2011). For example, the implementation of a certain reappraisal might become implicit in a reoccurring situation (Gyurak et al., 2011), resulting in a reduced need for prefrontal control. As research on emotional learning suggests, particularly, the dlPFC might be less involved in implicit emotion regulation because these processes happen more automatically and require less cognitive control. For example, fear extinction is a learning process where an organism learns that a stimulus that was previously associated with a threat is no longer predicting this aversive event. Indeed, reduced fear expression after fear extinction seems to be the result of a direct inhibition of the amygdala by the vmPFC rather than the dlPFC (Milad & Quirk, 2002; Phelps, Delgado, Nearing, & LeDoux, 2004).

Tremendous research across species has focused on fear extinction to diminish a previously acquired fear response (Pavlov, 1927; Phelps et al., 2004; LaBar et al., 1998; Tavote, Fadok, & Lüthi, 2015). However, the question remains whether the fear response is briefly diminished and the fear expression is only inhibited or whether it has permanently disappeared. The answer depends on the possibility to change the underlying fear memory. In order to prevent future harm and sustain survival, it is adaptive to form strong, long-lasting and coherent fear memories after as few as possible learning experiences. That is in line with the traditional view of memory, according to which, memories are consolidated after an initial learning experience and are basically resistant to change once this consolidation is terminated (see Figure 2; McGaugh, 2000; Squire & Davis, 1981). Indeed, the diminished fear response after standard fear extinction is not permanent, but returns after reinstatement, spontaneous recovery or renewal (Bouton, 2004).

Fear responses need to be flexible to adjust to changing situations. Otherwise fear

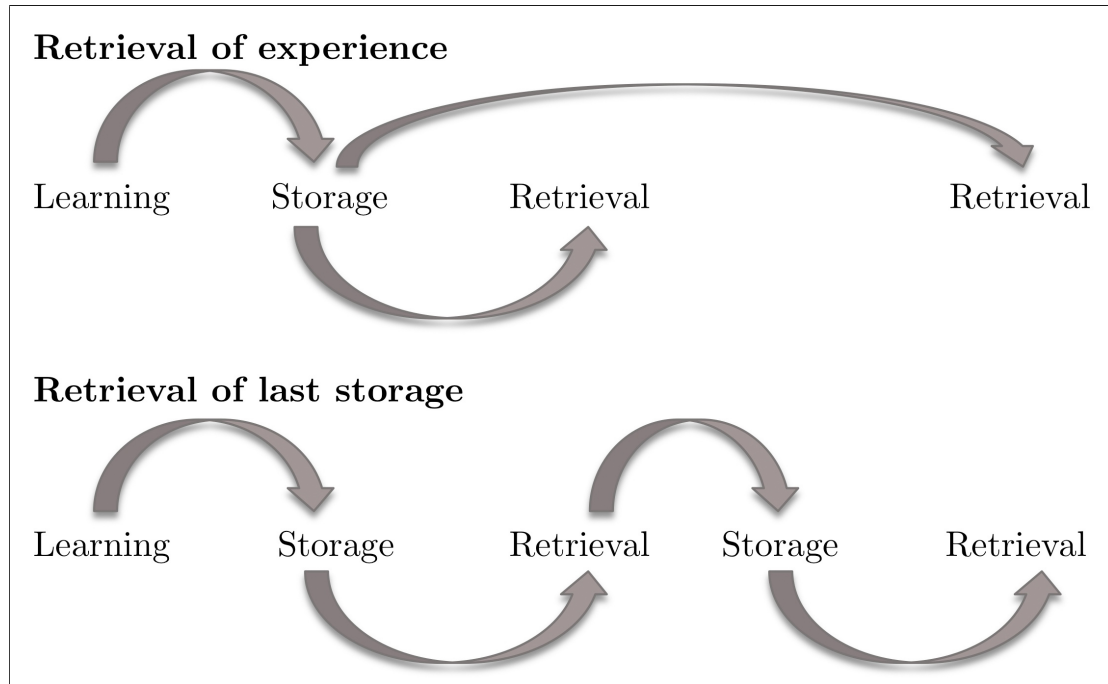


Figure 2: Two views of memory. Adapted from Memory Reconsolidation (Alberini & LeDoux, 2013).

becomes pathological, as in anxiety disorders where fear networks<sup>2</sup> are rigid, withstand alterations (Foa & Kozak, 1985) and involve strong response elements (Lang, McTeague, & Bradley, 2014; Mennin, Heimberg, Turk, & Fresco, 2005). Therefore,

<sup>2</sup>According to Lang (1979) emotions are represented in propositional networks with stimulus, response, as well as meaning propositions. Stimulus propositions are conceptualized as perceived information about the physical properties of a given stimulus, e.g., its colour, size, smell and texture. Response propositions are modality specific; they reach from adjustments of the sensory organs (e.g., focussing the pupil to detect some detail of the stimulus), to somato-visceral changes (e.g., increasing the heart rate to prepare for the escape from threat) and motor responses (e.g., running away from a threat). Meaning propositions are interpretations or appraisals of the stimulus meaning depending on the individual knowledge and experience with the stimulus. Specific for emotions, in contrast to cognitions, is the association of the propositional network with a motivational circuit. This circuit consists of two systems: (1) an appetitive system associated with pleasant affect and preservation (e.g., feeding) (2) an aversive system associated with unpleasant affect and protection (e.g., flight from predators; Lang et al., 1997). The affective valence of the resulting emotion (pleasant or unpleasant) is determined by the motivational system that is mainly activated (Lang & Bradley, 2010). In addition to the valence dimension, emotions can be characterized by an arousal dimension, which reflects the urgency to act in response to the stimuli and determines the extent of the response mobilisation and thereby the intensity of the resulting emotion (Lang & Bradley, 2010). The activation of the motivational circuit leads to adjustments of the sensory and motor system with the aim to preserve the survival of the organism (Lang et al., 1997). Hence, emotions are considered dispositions to act according to a motivational state (Lang et al., 1997).

it is crucial that the underlying memory structures can integrate new information.

Recently, one line of research evolved, examining the reconsolidation update mechanism possibly underlying this flexibility of memories (Bentz & Schiller, 2015). In 2000, Nader and colleagues showed in rats that the fear response disappears when a protein synthesis inhibitor is injected directly into the amygdala after reactivation of the initial fear memory. Given that memory formation itself depends on protein synthesis this result implies: (1) memories become labile again after reactivation and need to undergo a renewed consolidation, termed reconsolidation; (2) if the reconsolidation of a fear memory is blocked pharmacologically the fear memory will disappear (Nader, Schafe, & LeDoux, 2000; see Figure 2). Accordingly, standard extinction might leave the original fear memory intact and lead to the formation of a new safety memory resulting in two memories competing for expression. In contrast, prior activation of the initial fear memory leads to an incorporation of the safety information resulting in one updated memory (Schiller & Phelps, 2011).

Based on this revolutionary finding, Schiller and colleagues (2010) were the first to develop a behavioral approach to update fear memories in humans during reconsolidation. To install a fear memory, they applied a standard fear conditioning paradigm. However, in contrast to applying a standard fear extinction paradigm to diminish the fear response, they reactivated the initial fear memory prior to the extinction. Following this procedure, Schiller and colleagues (2010) showed that, the fear response was diminished even after the reinstatement of fear. Thus the extinction information was indeed incorporated in the initial fear memory during reconsolidation, permanently altering the fear response (Schiller et al., 2010).

## **Study 2: Reconsolidation of fear memories**

This finding, however, has been hard to replicate (Golkar, Bellander, Olsson, & Öhman, 2012; Kindt & Soeter, 2011). Therefore, Steinfurth and colleagues (2014; see Manuscript 3, Appendix A), investigated the boundary conditions of the reconsolidation update mechanism (Auber, Tedesco, Jones, Monfils, & Chiamulera, 2014). They focused on older fear memories, since traumatic incidents often happen long before treatment is available (Steinfurth et al., 2013). The behavioral fear reconsolidation paradigm (Schiller et al., 2010) was extended to include two additional experimental groups with one-week-old fear memories. On the first day all subjects underwent fear conditioning in order to form a standardized fear memory (see

Figure 2). During the fear acquisition procedure an unconditioned stimulus (UCS, electric shock) was paired with a conditioned stimulus (CS+, yellow slide), another neutral stimulus (blue slide) was also presented but never paired with a shock (CS-). After a few pairings with the UCS, participants also exhibited a fear response to the CS+. On the second day, two subject groups —with one-day-old fear memories— returned to the lab. One group underwent standard extinction training in which the CS+ was presented multiple times without reinforcement typically resulting in a decreasing fear response. The other group received a reminder cue (an unreinforced CS+) to reactivate the fear memory prior to the same extinction training. The other two experimental groups returned to the lab after one week with one-week-old fear memories and underwent the same procedure: One group received standard extinction training, the other group received a reminder cue prior to standard extinction training. To test whether the fear response would return, all participants underwent a fear reinstatement procedure with four unsignalled UCS followed by a reextinction period (CS- and CS+). During all sessions participants' skin conductance responses were recorded (Steinfurth et al., 2014). This autonomic response reflects sympathetic arousal and can be used to infer on amygdala activity (Hamm, Weike, & Melzig, 2006; Phelps et al., 2001). The results showed that the fear response was diminished after fear reinstatement when fear extinction was conducted during reconsolidation compared to standard fear extinction for one-day-old and one-week-old fear memories. These findings replicate previous research using the same behavioral paradigm for one-day-old memories (Agren et al., 2012; Schiller et al., 2010). Furthermore, showing that fear expression was diminished when extinction training during reconsolidation was conducted one week after fear acquisition, supports the notion that fear memories can be altered one-week after the initial fear memory is consolidated. On a neurobiological level, the diminished fear response after extinction during reconsolidation is associated with reduced amygdala activity and less vmPFC activity after fear renewal or reinstatement compared to standard extinction (Schiller, Kanen, LeDoux, Monfils, & Phelps, 2013; Agren et al., 2012). The reduced amygdala activity suggests, that the initial fear memory has been effectively altered through extinction during reconsolidation (Schiller et al., 2013). Therefore, less prefrontal cortex activity is necessary to control the amygdala-driven fear response (Schiller et al., 2013).

## 4 Dysfunctional emotion regulation

As illustrated above, successful emotion regulation requires an effective interplay of subcortical and prefrontal brain areas. Accordingly, prefrontal cortex hypoactivation and/ or amygdala hyperactivation is associated with deficits in emotion regulation (Hilbert, Lueken, & Beesdo-Baum, 2014; Britton, Lissek, Grillon, Norcross, & Pine, 2011; Davidson, Putnam, & Larsen, 2000). As stated by the emotion dysregulation model of generalized anxiety disorder (GAD; Mennin et al., 2005), patients with GAD can be characterized by heightened emotional intensity, poor understanding of emotions, negative reactivity to emotions, and less ability to reassure oneself after negative emotions. Therefore, patients with GAD might try to avoid emotions. Indeed, they respond to potential future threats with worry, a state of anxious anticipation (Becker & Hoyer, 2005; Barlow, 2000) and key characteristic of GAD (APA, 2013).

To date, there are two competing theories regarding the function of worry. On one hand, the avoidance model of worry proposed by Borkovec (1994), according to which worry is a cognitive strategy to avoid intense emotions and physiological arousal. The suppression of vivid emotional imagery is thought to prevent successful habituation and thereby to reinforce the maintenance of worry (Foa & Kozak, 1986; Mowrer, 1947). On the other hand, the contrast avoidance model of worry by Newman and Llera (2011) suggests, that worry indeed elicits emotional arousal and is applied purposely to maintain a negative emotional state in order to prevent sharp, uncontrollable shifts of the affective state. In fact, here, worry is positively reinforced by the experience of more positive emotional contrasts (e.g., a positive surprise) than negative emotional contrasts.

The neurobiological and physiological findings supporting these theories are heterogeneous. Some studies observed indices of emotional activity (e.g., increased heart rate: Hofman et al., 2005; increased skin conductance response: Delgado et al., 2009) whereas others observed no such difference (e.g., no changes in heart rate: Borkovec & Hu, 1990; skin conductance response: Hoehn-Saric, Lee, McLeod, & Wong, 2005;

or even decreased BOLD activity in the amygdala: Hoehn-Saric et al., 2005; Paulesu et al., 2010). The diverse methodology of the reviewed studies might be one reason for the heterogeneity of the findings (e.g., personal or standardized stimuli, different durations of the worry periods, different comparison conditions, different levels of pathology of the participants). However, the main reason might be the incoherent and diffuse nature of the worry process itself with a high level of fluidity among the associated emotional response elements (Barlow, 2002; Lang, 1994).

### **Study 3: Worry and rumination**

In order to shed light on the neural correlates of worry and to distinguish whether the function is to reduce or to prolong unpleasant emotions, Steinfurth, Alius, Wendt, and Hamm (2017; see Manuscript 4, Appendix A) examined emotional activity during thinking about personal worries. Two experiments were conducted, one using fMRI to record BOLD activity in the brain and the other one to record autonomic changes (skin conductance, heart rate) and defensive reflex modulation (startle response). Furthermore, to investigate the specificity of changes another more dysfunctional<sup>3</sup> emotion regulation strategy, rumination<sup>4</sup>, was included. To induce worry and rumination, participants' personal topics were recorded prior to the experiment. During the experiment, participants were instructed to respond as they would naturally. The topics were presented with the according instructions "to worry" or "to ruminate".

The results showed that worrying about potentially aversive events in the future was associated with reports of higher anxiety and tension, increased skin conductance responses as well as a significant potentiation of the startle reflex compared to thinking about neutral events (Steinfurth et al., 2017). Similarly, rumination was associated with reports of stronger depression and tension, increased skin conduc-

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<sup>3</sup>The simple distinction of emotion regulation strategies as functional and dysfunctional is not sufficient. To capture the full spectrum of functionality an eight-factor structure is necessary: rumination, experience suppression, expressive suppression, avoidance, activity and social support, reappraisal, problem solving, and acceptance (Izadpanah, Barnow, Neubauer, Holl, 2017).

<sup>4</sup>Similar to worry, rumination is a process of unconstructive repetitive thought (Papageorgiou & Wells, 2001; Segerstrom, Tsao, Alden, & Craske, 2000; Watkins, 2008). However, the focus is on past mistakes, their causes and implications as well as an indulgence in negative affect associated with the preservation of depression (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). Since rumination strongly relies on self-referential processes, neurobiological activity during rumination has been observed in brain regions within the default mode network (Cooney, Joormann, Eugene, Dennis, & Gotlib, 2010; Raichle et al., 2001; Whitfield-Gabrieli & Ford, 2012).

tance response, as well as an initial potentiation of the startle reflex compared to thinking about neutral events. The heart rate was not significantly elevated during either thought process. The direct comparison between both strategies revealed a significantly prolonged potentiation of the startle response during worry. On a neurobiological level increased BOLD activity was observed in the insula, the anterior cingulate cortex (ACC), the hippocampus, the dlPFC, and the inferior temporal gyrus during worrying. Activity in similar brain areas was observed during rumination, however, neurobiological activity during rumination was generally increased compared to worry (Steinfurth et al., 2017).

The present results indicate that worry is associated with a prolonged emotional response. In particular, the increased BOLD activity in the insula and the potentiated startle response indicate a state of anxious apprehension. Thus, the function of worry seems to be, indeed, the prevention of abrupt and uncontrollable emotional shifts (Newman & Llera, 2011). Interestingly, the observed neurobiological activity during worry is less pronounced than during rumination. This might be due to the incoherent and diffuse nature of the worry process itself (Barlow, 2002). Furthermore, rumination's stronger capacity to invoke an emotional response is due to its focus on negative events that actually occurred in the past whereas the focus of worry is on potentially occurring negative events in the future. Indeed, it has been shown that rumination strongly relies on autobiographical memory (Burgess, Maguire, & Keefe, 2002; Cooney et al., 2010) and that physiological responses get less clear when there is no original experience of the negative event (Lang, 1979) and are the least when the task is not even 'to imagine' but only 'to think about' emotional material (Vrana, Cuthbert, & Lang, 1989).

Additionally, both strategies were associated with increased activity in brain areas within the default mode network. The default mode network has been shown to be active when individuals are focused on internal processes or self-referential mental simulations, including thinking about ones past or future, or thinking about the response of others (Buckner, Andrews-Hanna, & Schacter, 2008). Thus increased activity of the default mode network underscores the idea that worry and rumination are self-referential, repetitive thought processes.



## 5 Integrative summary and future directions

The present thesis focused on explicit (Study 1), implicit (Study 2) and dysfunctional (Study 3) emotion regulation using neurobiological, autonomic and behavioral measures. In this summary, the main results and the reviewed literature are integrated into a neurobiological model of emotion regulation (see Figure 3).

First, emotion induction was associated with behavioral, autonomic and neurobiological activity indicative of emotional responses: Participants responded with higher BOLD activity in the amygdala and higher subjective emotionality to the presentation of emotional pictures (Study 1). Similarly, in Study 2, participants showed an increased autonomic response to the conditioned stimulus, which is modulated by the amygdala via the brain stem (Hamm et al., 2006).

Second, successful explicit and implicit emotion regulation resulted in decreased BOLD activity in the amygdala (Study 1) and a decreased autonomic response (Study 2). This bidirectional modulation was associated with dlPFC activity during both types of explicit emotion regulation, most likely in accordance with other prefrontal areas, for example, the ACC, dorsomedial PFC, and ventrolateral PFC (Buhle et al., 2013; Carter et al., 2000; Ochsner et al., 2012). During implicit emotion regulation no neurobiological data were collected, however, a decreased autonomic fear response indicating decreased amygdala activity was observed. Additionally, previous research suggests, that the medial PFC might be responsible for the modulation of amygdala activity during implicit emotion regulation (Gyurak et al., 2011). In particular, research on reconsolidation (Agren et al., 2012; Schiller et al., 2013) and on fear extinction (Milad et al., 2007; Kalisch et al., 2006; Hartley & Phelps, 2010; Phelps et al., 2004) suggests, that the reduced fear response is modulated by the vmPFC. This modulation is thought to be abundant after fear extinction during the reconsolidation window, since the original fear memory has been altered and the stimuli have lost the capacity to elicit a fear response (Schiller & Phelps, 2011).

Third, dysfunctional emotion regulation can be characterized by some amount of neurobiological, autonomic and behavioral activity characteristic for emotion generation. Anxiety-related future-oriented worry was associated with increased BOLD activity in the insula and a fear potentiated startle. Furthermore, increased BOLD activity in the amygdala was observed during past-oriented rumination on negative personal events. Furthermore, increased BOLD activity in the prefrontal cortex and other brain areas of the default mode network was observed. These findings support the notion, that both strategies are characterized by an indulgence in self-referential negative thought and preserve rather than diminish negative emotions. Finally, all three studies support the notion that emotion generation and emotion regulation are not distinct but highly interrelated processes (Ochsner et al., 2012).

In summary, the results of the present thesis suggest that implicit and explicit emotion regulation can be effective in regulating ones' emotions. However, they might rely at least partly on different neurobiological pathways. To deepen the understanding of these two types of emotion regulation and allow for better categorization of the applied paradigms, more recent research tries to describe them with computational approaches. Within this computational and mechanistic framework emotion regulation can be described with regards to the decisional control involved as either more model-free or more model-based control (Etkin, Büchel, & Gross, 2015). The main distinction is whether prior knowledge is required or, if decisions are rule-based (model-based control) or not with behavior being guided by experienced prediction errors (model-free control; Etkin et al., 2015). This new computational approach might be useful to distinguish different subprocesses and the interaction between implicit and explicit emotion regulation, thus facilitating detailed analyses of emotion regulation deficits and providing a foundation for precise therapeutic interventions aiming at regaining emotional competence.

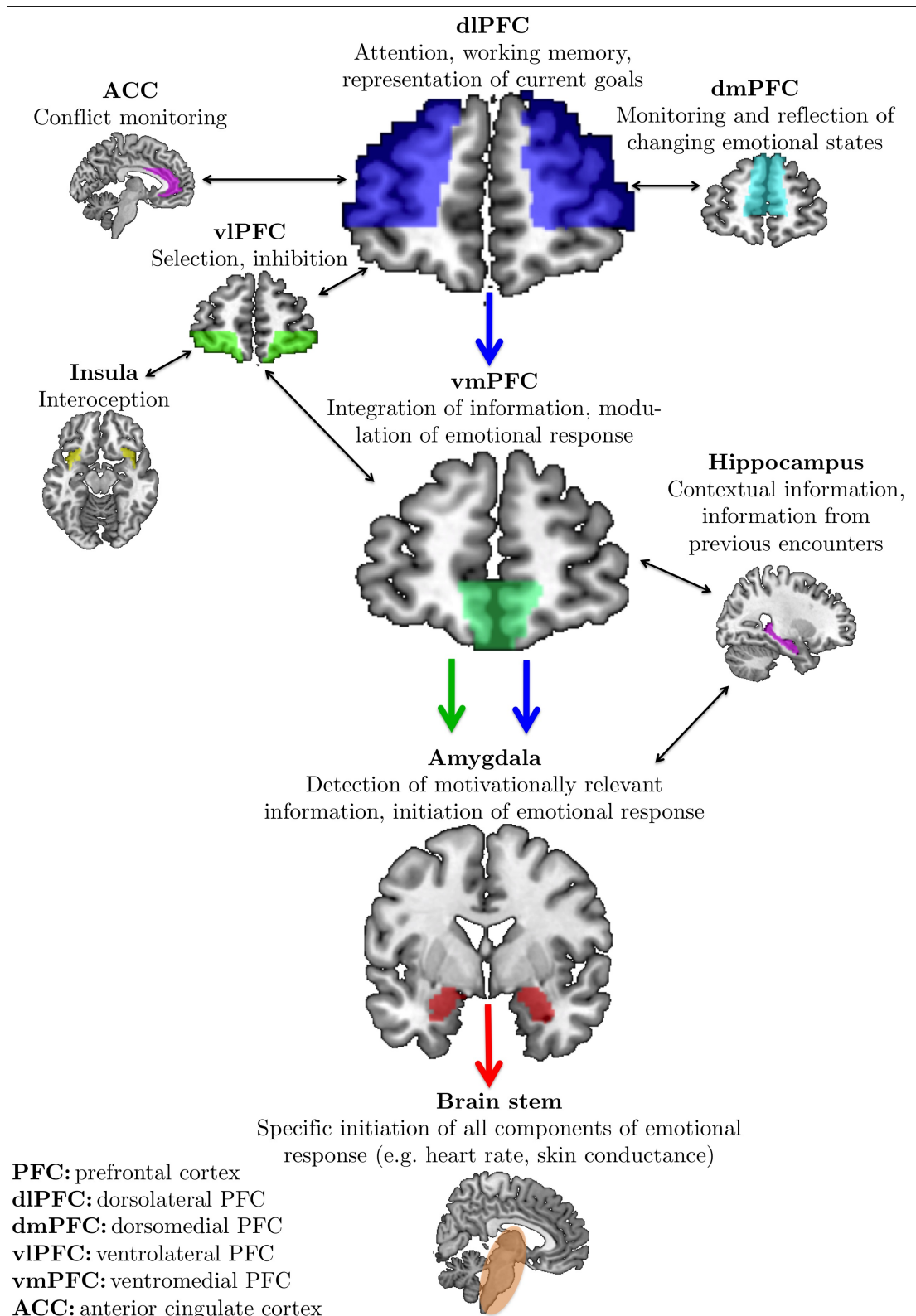


Figure 3: Neurobiological model of emotion regulation. The amygdala is suggested to initiate the emotional response via the brain stem (red arrow). Explicit emotion regulation modulates this response by prefrontal regulatory mechanisms (blue arrows). Implicit emotion regulation relies on the vmPFC (green arrow). Dysfunctional emotion regulation is associated with increased prefrontal and subcortical brain activity.



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# Appendix A: Publications in peer-reviewed journals

## Study 1:

Steinfurth, E. C. K., Wendt, J., & Hamm, A. O. (2013). Neurobiologische Grundlagen der Emotionsregulation. *Psychologische Rundschau*, 64(4), 208–216.

Steinfurth, E. C. K., Wendt, J., Geisler, F., Hamm, A. O., Thayer, J. F., & Koeing, J. (in prep.). Resting state high-frequency heart rate variability is associated with neural activity during explicit emotion regulation.

## Study 2:

Steinfurth, E. C. K., Kanen, J. W., Raio, C., Clem, R., Huganir, R. L., & Phelps, E. A. (2014). Young and old pavlovian fear memories can be modified with extinction training during reconsolidation in humans. *Learning and Memory*, 21, 338–341.

## Study 3:

Steinfurth, E. C. K., Alius, M. G., Wendt, J., & Hamm, A. O. (2017). Physiological and neural correlates of worry and rumination: Support for the contrast avoidance model of worry. *Psychophysiology*, 54(2), 161–171.



# Study 1

## Neurobiologische Grundlagen der Emotionsregulation

Elisa C. K. Steinfurth, Julia Wendt, & Alfons O. Hamm

*Psychologische Rundschau*, 64(4), 208–216.

Published in 2013

Author contributions:

AH, JW, and ES designed the study, ES did the laboratory assessment, ES preprocessed and analyzed the data under supervision of JW. All authors contributed to the interpretation of the data and wrote the manuscript (first draft provided by ES).



# Neurobiologische Grundlagen der Emotionsregulation

Elisa Steinfurth, Julia Wendt und Alfons Hamm

**Zusammenfassung.** Es gehört zu den zentralen menschlichen Fertigkeiten, Emotionen, welche durch externe oder interne Ereignisse ausgelöst werden gemäß der kurz- und langfristigen Handlungsziele zu regulieren. Diese Fertigkeiten werden über neuronale Netzwerke im präfrontalen Kortex vermittelt. Der dorsolaterale und ventromediale präfrontale Kortex ist entscheidend beteiligt, wenn Menschen über Neubewertung der Situation versuchen ihre Emotionen kognitiv zu modulieren. Die neuronalen Netzwerke dieser präfrontalen Kortexareale hemmen dabei die Aktivität der Amygdala und reduzieren somit die Signifikanz des emotionsauslösenden Ereignisses. Emotionsregulation wird daher als Zusammenspiel von emotionsgenerierenden Regionen (z. B. Amygdala, Insel etc.) und regulierenden Kontrollregionen (z. B. dorsolateraler und ventromedialer präfrontaler Kortex) betrachtet.

Schlüsselwörter: Emotion, Emotionsregulation, Kognitive Neubewertung, Amygdala; Präfrontaler Kortex

## Neurobiological basis of emotion regulation

**Abstract.** One of the most central human skills is the ability to regulate emotions that are elicited by external or internal events depending on the situational demands and the organism's short- or long-term goals. These skills are mediated by neural networks located in prefrontal brain areas. The dorsolateral cortex and the ventromedial prefrontal cortex play a crucial role in the cognitive regulation of emotions, particularly when individuals reappraise the emotional event. The neural networks of the prefrontal area inhibit the activation of the amygdala, the core structure for detecting emotionally significant stimuli in the environment, thus decreasing the emotional salience of an activating event. Emotion regulation can therefore be considered as an interplay of regions contributing to the generation of emotions (e. g., amygdala, insula) and cognitive regions (e. g., dorsolateral and ventromedial prefrontal cortex) that are involved in top-down control but also in the monitoring of emotional events. Different strategies (e. g., reappraisal) can be applied to effectively increase or decrease amygdala activity.

Key words: emotion, emotion regulation, reappraisal, amygdala, prefrontal cortex

Die Fähigkeit, die eigenen Emotionen entsprechend situativer Anforderungen und persönlicher Handlungsziele zu regulieren, ist grundlegend für ein erfolgreiches Zusammenleben in einem sozialen Umfeld. Würden Emotionen jederzeit ungefiltert zum Ausdruck gebracht wären Streit und Missverständnisse unumgänglich und langfristige Ziele für den Einzelnen kaum erreichbar. Die meisten Menschen lernen im Laufe ihres Lebens, ihre Emotionen mehr oder minder gut zu regulieren. Problematisch wird es erst, wenn Emotionen so intensiv sind, dass sie nicht mehr reguliert werden können oder Regulationsstrategien nicht mehr funktionieren. Viele psychopathologische Phänomene sind durch eine Störung der Emotionsregulationsfähigkeit gekennzeichnet. Patienten mit Angsterkrankungen leiden beispielsweise unter der Intensität oder Generalisierung ihrer Angst, die sie nicht mehr in den Griff bekommen, und beginnen deshalb zunächst einzelne und dann immer mehr Situationen zu vermeiden.

## Emotion und Emotionsregulation

Aus neurobiologischer Perspektive sind Emotionen kein Epiphänomen subjektiver Gefühlserlebnisse, sondern

führen als Antwort auf externe oder interne Reize darüber hinaus zu beobachtbaren Verhaltensänderungen, die von neurophysiologischen und endokrinen Reaktionen begleitet sind. Diese Veränderungen bereiten den Körper darauf vor, möglichst effektiv in einem bestimmten Kontext zu handeln. Funktionell betrachtet sind Emotionen daher Handlungsdispositionen, die das aktuelle Verhalten und mentale Prozesse unterbrechen (Frijda, 1986; Lang, Bradley & Cuthbert, 1997). Daher implizieren Emotionen immer eine Handlungsrichtung, d. h. auf der Ebene des Erlebens sind Emotionen immer positiv oder negativ getönt (sind also angenehm oder unangenehm). Auf der Verhaltensebene kovariiert diese emotionale Tönung mit der motivationalen Komponente, der Annäherung oder der Vermeidung (Lang, Bradley & Cuthbert, 1990). Das emotionale System ist also stark mit dem biphasisch organisierten Motivationssystem assoziiert, daher formen Valenz und Erregung die grundlegenden strategischen Dimensionen von Emotion (vgl. Hamm, Schupp & Weike, 2009). Dieses neurobiologische Modell der Verankerung emotionaler Prozess in basale aversive und appetitive Motivationssysteme, inklusive der sie steuernden neuronalen Netzwerke, ist nicht inkompatibel mit den kognitiven Bewertungstheorien. Gehen diese

doch davon aus, dass die emotionsauslösende Wirkung bzw. die motivationale Bedeutung von Reizen erst durch ihre Bewertung entsteht, wobei mindestens zwei sequentielle Bewertungsprozesse angenommen werden.

Der erste Prozess ist die relativ automatische Bestimmung der affektiven Relevanz eines Reizes. Im zweiten Prozess geht es um die Bestimmung der kontextuellen Bedeutung und der Angemessenheit möglicher Reaktionen also die Regulation emotionaler Reaktionen in einem bestimmten Kontext (Anpassung des Emotionsausdrucks und der Regulation der Emotionsintensität; Gross, 1998; Lazarus, 1991). Das Konstrukt der Emotionsregulation umfasst daher den Einsatz unterschiedlicher Strategien wie die systematische Veränderung der Aufmerksamkeit auf den Reiz, die Neubewertung des Reizes oder auch die Veränderung der Reaktion, die durch den Reiz aktiviert wird (Goldin, McRae, Wiveka & Gross, 2008). Je nachdem, wann der Emotionsentstehungsprozess beeinflusst wird, werden fünf Gruppen von Emotionsregulationsstrategien unterschieden (Gross, 1998). Die Hauptunterscheidung liegt hierbei darin, ob die Emotionsregulationsstrategien eingesetzt werden, *bevor* oder *nachdem* affektive Bewertungsprozesse abgeschlossen wurden und Emotionen distinkte Reaktionstendenzen sind (Gross & Munoz, 1995). In Abhängigkeit vom Zeitpunkt ihres Einsatzes im Emotionsentstehungsprozess werden Emotionsregulationsstrategien daher entweder als Antezedenz-fokussierte oder als Reaktions-fokussierte Strategien bezeichnet (Gross, 1998). Je nachdem, wie und zu welchem Zeitpunkt der Bewertungszyklus beeinflusst wird, werden die Antezedenz-fokussierten Strategien weiter differenziert. (Gross, 1998).

## Neurobiologie der Emotionsregulation

Durch den Einsatz funktioneller Kernspintomographie ist es heutzutage möglich zu untersuchen, welche neuronalen Schaltkreise aktiviert werden, wenn man Personen instruiert, ihre Emotionen in eine bestimmte Richtung zu regulieren. In den letzten Jahren wurde dabei vor allem untersucht, welche Netzwerke aktiviert sind, wenn Menschen aufgefordert werden, ihre Emotionen durch eine *kognitive Neubewertung* zu regulieren (siehe Ochsner, Silvers & Buhle, 2012). Die kognitive Neubewertung ist eine Antezedenz-fokussierte Emotionsregulationsstrategie. Sie beinhaltet die aktive Veränderung der Bedeutung einer Situation und ihres emotionalen Gehalts (Gross & Thompson, 2007) und ist eine der flexibelsten und effektivsten Strategien zur Reduktion negativer Auswirkungen eines aversiven Ereignisses (Ochsner, Bunge, Gross & Gabrieli, 2002). Bei diesen Studien werden in der Regel emotionsauslösende Reize präsentiert (z. B. Bilder oder Filme) und die Probanden erhalten die Instruktion, ihre Emotion entweder zu verstärken, indem sie sich vorstellen persönlich in die Szene invol-

viert zu sein, oder sich selbst aktiv von der Szene zu distanzieren und somit die emotionale Reaktion zu reduzieren. Bei dieser Regulationstaktik wird somit die Selbstfokussierung moduliert. Eine andere Form der Regulation ist eher situationsfokussiert und wird als Reinterpretation bezeichnet. Hier werden die situativen Elemente der emotionsauslösenden Situation umgedeutet (vgl. Ochsner et al., 2012). Die Hirnregion, deren Aktivität klassischer Weise als Indikator des Regulationserfolgs verwendet wird, ist die Amygdala. Nachdem die Amygdala lange als Zentrum der Furchtverarbeitung diskutiert wurde (LeDoux, 1996), konnten neuere Untersuchungen zeigen, dass die Amygdala eben nicht nur mit Furcht assoziiert ist, sondern auch bei der Verarbeitung interessanter angenehmer Reize vermehrt aktiviert wird (Hamann, Ely, Grafton & Kilts, 1999; Sabatinelli, Lang, Keil & Bradley, 2007; Wendt, Lotze, Weike, Hosten & Hamm, 2008). Zudem zeigt eine Vielzahl von Studien, dass die Amygdala sehr zuverlässig durch Bilder emotionaler Gesichtsausdrücke aktiviert wird, obwohl diese Reize keine starken Furchtreaktionen auslösen (Adolphs & Spezio, 2006). Schließlich habituiert die Amygdala-Aktivierung sehr schnell (Phelps & LeDoux, 2005; Wendt, Schmidt, Lotze & Hamm, 2012) bei Präsentation eines neuen Reizes der gleichen Kategorie (z. B. ein neues Bild einer Spinne) kommt es jedoch sofort zu einer erneuten starken Aktivierung der Amygdala. Diese Befunde deuten darauf hin, dass die Amygdala eine zentrale Rolle bei der Selektion emotional relevanter distaler Reize spielt und dem Gehirn signalisiert, welche Reize bevorzugt verarbeitet werden sollten. Dieses Absuchen der Umgebung nach emotional relevanten Reizen geschieht eher automatisiert und scheint nicht abhängig vom gegenwärtigen Aufmerksamkeitsfokus zu sein. Die verstärkte Aktivierung der Amygdala durch emotional bedeutsame Reize ist erhöht, unabhängig davon, ob die Probanden instruiert wurden, auf diese Reize zu achten oder nicht (Vuilleumir, 2009). Dennoch kann die Amygdala-Aktivierung durch die Instruktion, sich in die emotionale Szene hineinzusetzen oder sich von ihr zu distanzieren, moduliert werden (Eippert, Weiskopf, Birbaumer & Anders, 2007; Schaefer et al., 2002).

Neben der Amygdala wird bei der Verarbeitung emotionaler Reize zuverlässig der insuläre Kortex aktiviert. Im insulären Kortex konvergieren alle viszerale Afferenzen sowie die Schmerz- und Wärmereize, was darauf hindeutet, dass der Inselrinde eine zentrale Rolle bei der Repräsentation interozeptiver Reize zukommt. Besonders die vordere Inselrinde wird mit dem subjektiven Erleben von Emotionen in Zusammenhang gebracht (Craig, 2002) und zwar vor allem durch ihre Rolle bei der Überwachung autonomer Erregung (Critchley, Corfield, Chandler, Mathias & Dolan, 2000; Critchley, Wiens, Rotshtein, Öhman & Dolan, 2004).

Die Amygdala und die vordere Inselrinde spielen also bei der Emotionsentstehung eine entscheidende Rolle.

Dieses emotionsgenerierende System steht unter dem modulierenden Einfluss von kognitiven Systemen, die für die Regulation von Emotionen verantwortlich gemacht werden. In einer Vielzahl von Bildgebungsstudien bei denen Probanden instruiert wurden, ihre emotionalen Reaktionen (hauptsächlich negative Emotionen) zu reduzieren (z.B. durch Neubewertung, Reaktionsunterdrückung oder Ablenkung), wurde stets eine vermehrte Aktivierung des präfrontalen Kortex gefunden (Beauregard, Levesque & Bourgin, 2001; Ochsner & Gross, 2005; Phan et al., 2005). Ochsner und Mitarbeiter (2012) unterscheiden drei neuronale Systeme, die bei der kognitiven Neubewertung eine Rolle spielen: (1) der *ventrolaterale* präfrontale Kortex, der mit der Auswahl zielführender und Stimulus-angemessener Reaktionen und der Hemmung unangemessener emotionaler Reaktionen assoziiert wird, (2) der *dorsolaterale* und posteriore präfrontale Kortex, der für die Aufmerksamkeitslenkung auf die neu zu bewertenden Aspekte des Reizes zuständig ist und dafür, das Regulationsziel im Gedächtnis zu behalten und (3) der *dorsale Teil des anterioren Cingulums*, für den eine Rolle bei der Überwachung der Auswirkungen der aktuellen kognitiven Neubewertung angenommen wird (Phillips, Ladouceur & Drevets, 2008). Um die an der Emotionsregulation beteiligten Strukturen genauer zu verdeutlichen und auch die in dieser Forschung typischerweise verwendete experimentelle Methodik darzustellen möchten wir eine Studie aus dem eigenen Labor exemplarisch berichten und die Kernbefunde dieser neurobiologischen Emotionsregulationsforschung herausarbeiten.

## Empirische Evidenz

Ziel unserer Studie war es, die neuronalen Netzwerke zu untersuchen, die mit der Regulationsrichtung (Steigerung vs. Verringerung), der Valenz der ausgelösten Emotionen (angenehm vs. unangenehm) sowie mit der verwendeten Strategie (Antezedenz- vs. Reaktions-fokussierte Strategie) assoziiert sind. Als Beispiel für eine Antezedenz-fokussierte Strategie untersuchten wir die kognitive Neubewertung. Kognitive Neubewertung ist eine kognitiv-linguistische Strategie (Goldin et al., 2008), die auf der Veränderung der kognitiven Repräsentation eines Ereignis basiert (Gross & Thompson, 2007). Im Gegensatz zu anderen Strategien – beispielsweise der Unterdrückung des Emotionsausdrucks – ist die kognitive Neubewertung mit weniger sozialen, physiologischen und psychologischen Kosten verbunden (Richards & Gross, 2000). Kognitive Neubewertung führt außerdem zu einer Reduktion des negativen Emotionsausdrucks, aber nicht zu einer Reduktion der Intensität positiver emotionaler Reaktionen (Gross, 2001) (siehe Barnow, Aldinger et al., in diesem Heft). Wir wollten die kognitive Neubewertung mit einer reaktionsfokussierten Strategie vergleichen (vgl. Goldin et al., 2008). Die Reaktionsmodulation wird verwendet, wenn die Bewertungsprozesse abgeschlossen sind und die

Emotion sich voll entfaltet hat (Gross, 1998). Daher umfasst sie die Beeinflussung des emotionalen Ausdrucks und der körperlichen Symptome (Atemfrequenz und Körperspannung).

## Methode

Zwölf weibliche und 12 männliche Studierende regulierten ihre Emotionen mit zwei verschiedenen Strategien (Kognitive Neubewertung und Reaktionsmodulation). Diese Strategien wurden vor der fMRT-Studie trainiert und während der Untersuchung in zwei separaten Blöcken zur Emotionsregulation angewendet. Ausgelöst wurden die Emotionen durch 36 angenehme und 36 unangenehme Bilder, die dem „*International Affective Picture System*“ (IAPS; Lang, Bradley & Cuthbert, 2005) entnommen wurden. Zwölf neutrale Bilder wurden als Vergleichsreize verwendet. Die angenehmen und unangenehmen Bilder waren hinsichtlich der Normwerte der ausgelösten Erregung ausbalanciert. Es wurde ein ereigniskorriertes Design verwendet. In jedem Durchgang wurde nach der 2.5 Sekunden dauernden Bildpräsentation für 0.5 s die Regulationsrichtung angezeigt. Nach der folgenden sechs sekundigen Regulationsphase wurden die Valenz- und Erregungsurteile abgefragt (siehe Abb. 1). Die Urteile wurden mit Hilfe des Selbstbewertungs-Männchens abgegeben (SAM; Bradley & Lang, 1994).

Bei der kognitiven Neubewertung sollte der Emotionsentstehungsprozess moduliert werden, z.B. durch Variation des persönlichen Bezugs zum Bildinhalt. Um eine Emotion zu verstärken, sollten die Versuchspersonen sich vorstellen, dass die auf dem Bild dargestellte Szene eine reale Situation ist, in der sie entweder persönlich oder eine ihnen nahestehende Person involviert sind. Um eine Emotion zu reduzieren sollten sich die Teilnehmer dagegen vorstellen, die Szene wäre nur gestellt oder sie wären ein unbeteiligter Beobachter.

Bei der Reaktionsmodulation sollte eine bewusste Veränderung der physiologischen Ausdruckskomponenten der Emotion (Atmung, körperliche Anspannung und Mimik) vorgenommen werden. Entweder sollte die emotionale Reaktion verstärkt (z.B. durch die Intensivierung der Atmung oder der körperlichen Anspannung oder durch eine Verstärkung des emotionalen Gesichtsausdrucks) oder reduziert werden (z.B. durch eine Verlangsamung der Atmung, eine Entspannung des Körpers oder eine Unterdrückung des emotionalen Gesichtsausdrucks). In Abbildung 1 ist das in dieser Studie verwendete Design dargestellt. Der nach oben gerichtete Pfeil gibt an, dass die Probanden in dieser Bedingung ihre Emotionen steigern sollten. Wenn die Emotion reduziert werden sollte, war der Pfeil nach unten gerichtet, sollten keine Emotionsregulationsstrategien eingesetzt werden, wurde ein Gleichheitszeichen gezeigt.

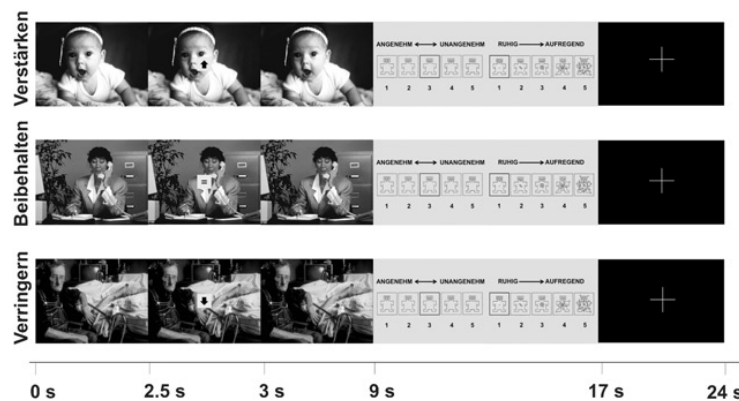


Abbildung 1. Darstellung der Versuchsanordnung: Angenehme und unangenehme Bilder wurden entweder mit der Instruktion Verstärken (Pfeil nach oben, obere Reihe), Beibehalten (Gleichheitszeichen, mittlere Reihe) oder Verringern (Pfeil nach unten, untere Reihe) dargeboten. Neutrale Bilder wurden immer mit einem Gleichheitszeichen präsentiert. Nach der Emotionsinduktionsphase (2,5 s), wurde die Regulationsrichtung angezeigt (Richtungspfeil bzw. Gleichheitszeichen) (1,5 s). Danach sollte für 6 s die Emotion entsprechend der angezeigten Instruktion reguliert werden. Unmittelbar im Anschluss wurde das emotionale Erleben eingestuft.

Die MRT-Daten wurden mit einem 1.5 T Scanner (Siemens Magnetom Symphony System), der mit einer 8-Kanal-Kopfspule ausgestattet war, erhoben. In einem Regulationsblock wurden jeweils 506 funktionelle T2\*-gewichtete Bilder in transversaler Richtung mit echoplanarer Bildgebung (EPI) aufgenommen (Repetitionszeit (TR)= 4 s, Field of View (FoV)= 192 mm, Matrix= 128 × 128, Flipwinkel= 90°, Echozeit (TE)= 38 ms). Jedes funktionelle Volumen umfasste 33 Schichten (Voxelgröße: 1.5 × 1.5 × 3 mm). Zwischen den Regulationsblöcken wurde ein hochauflöser anatomischer T1-gewichteter Scan mit einer TR von 11 ms durchgeführt (176 sagittale Schichten, FoV= 256 mm (Matrix = 256 × 256), TE= 5.2 ms, Voxelgröße: 1 × 1 × 1 mm). Die MRT Daten wurden mit der *Statistical Parametric Mapping* Software (SPM8, Wellcome Department of Imaging Neuroscience, London, UK) vorverarbeitet und analysiert. Die funktionalen Bilder wurden für den Aufnahmezeitpunkt und Bewegungen korrigiert, auf die anatomischen Bilder ko-registriert, segmentiert, räumlich normalisiert und an das Standardbild des Montreal Neurological Institute (MNI) angepasst und geglättet (FWHM 6 mm).

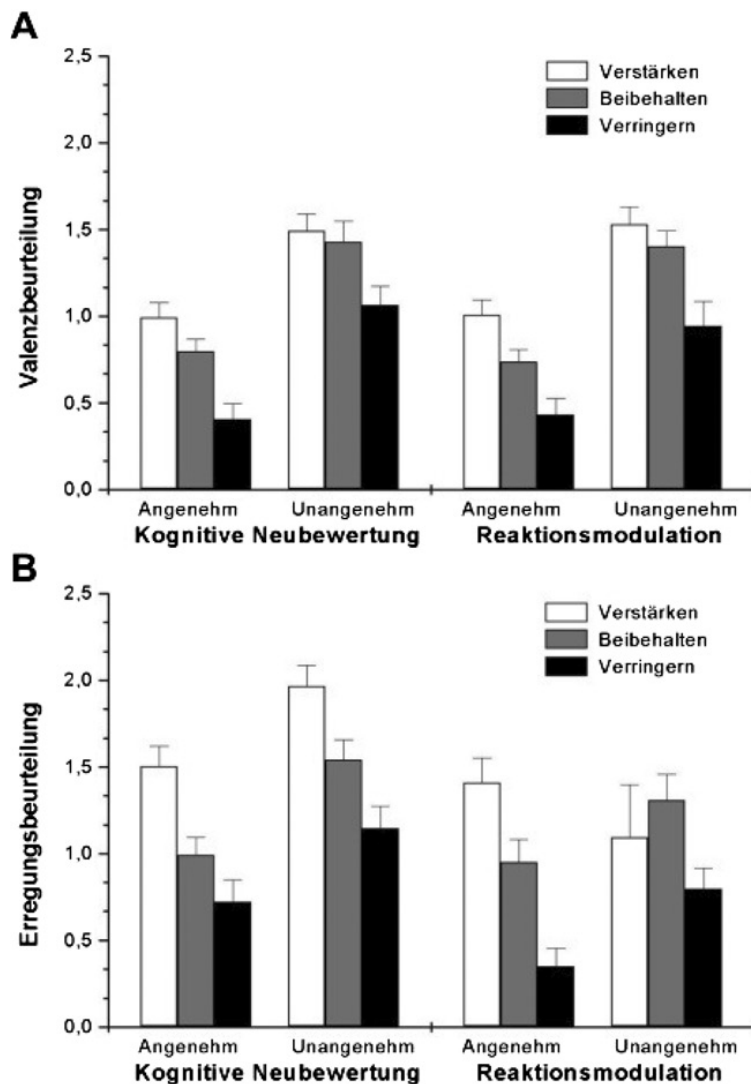
Für jeden Teilnehmer wurde ein Allgemeines Lineares Model mit je drei Regressoren spezifiziert: Emotionsinduktion, Emotionsregulation und Beurteilung. Für die Gruppenanalyse wurde eine Varianzanalyse mit den Faktoren Strategie (Kognitive Neubewertung, Reaktionsmodulation), Valenz (positiv, negativ) und Regulationsrichtung (verstärken, beibehalten, reduzieren) berechnet (*Full Factorial Model*). Außerdem wurden folgende gerichtete T-Tests berechnet: Regulieren > Beibehalten, Verstärken > Beibehalten und Verringern > Beibehalten. *Region of Interest* (ROI) Analysen wurden für die Amygdala durchgeführt. Die Amygdala wurde mit Hilfe einer auto-

matischen anatomischen Erkennungssoftware identifiziert (*Automated Anatomical Labeling* (AAL), Tzourio-Mazoyer et al., 2002). Aufgrund der ausgewiesenen Rolle des präfrontalen Kortex in der Emotionsregulation wird diese Region ebenfalls fokussiert betrachtet.

## Ergebnisse und Diskussion

Die Beurteilungen der emotionalen Reize nach jeder Regulation zeigen, dass die Emotionsregulation erfolgreich war. Abbildung 2 zeigt die Valenz (A) und die Erregungsbeurteilung (B) in Abhängigkeit der Regulationsrichtung und -strategie. Im Einklang mit bisherigen Ergebnissen (z. B. Kim & Hamann, 2007) wurden die Reize, bei denen die Emotionen gesteigert werden sollten, als jeweils angenehmer bzw. unangenehmer und erregender eingestuft. Entsprechend wurden die gleichen Reize als weniger angenehm bzw. unangenehm und weniger erregend eingestuft wurden, wenn die Probanden aufgefordert wurden, ihre Emotionen zu reduzieren. Dieses Muster wurde ohne Unterschied bei beiden Regulationsstrategien beobachtet (Bebko, Franconeri, Ochsner & Chiao, 2011; Goldin et al., 2008; Gross & Levenson, 1997).

Um zu überprüfen, ob es gelungen war mit unserer Versuchsanordnung Emotionen auszulösen, verglichen wir die Hirnaktivität während der Emotionsinduktionsphasen, in der nur das emotionale Bild präsentiert wurde, aber noch keine Instruktion über die Richtung der Emotionsregulation gegeben wurde. ROI-Analysen ergaben, dass die Aktivität in der Amygdala während der Betrachtung positiver und negativer Bilder im Vergleich zu neutralen Bildern zuverlässig verstärkt war. Daher können wir nun die Veränderung der Amygdala Aktivität als In-



*Abbildung 2.* Beurteilungen der Reize nach der Regulation. A zeigt die Valenzbeurteilungen und B zeigt die Erregungsbeurteilungen. Dargestellt ist jeweils die absolute Differenz zum Mittelwert der Beurteilung von neutralen Reizen.

dikator für den Regulationserfolg betrachten. In Abbildung 3 ist die Aktivierung der Amygdala zu sehen, die mit der Regulationsrichtung assoziiert ist. Wenn die Probanden instruiert waren, die emotionale Szene neu zu bewerten und sich in die Situation hineinzusetzen, kam es zu einer deutlichen Steigerung der Amygdala Aktivität. Lautete die Instruktion dagegen, sich von der emotionalen Szene zu distanzieren, führte dies zu einer deutlichen Reduktion der Amygdala-Aktivierung. Diese Befunde decken sich mit den Ergebnissen anderer Arbeitsgruppen (Eippert et al., 2007; Urry et al., 2006). Analoge Ergebnisse ergaben sich auch bei der anderen Regulationsstrategie, d.h. wenn die Emotionen durch Unterdrückung bzw. Verstärkung des Emotionsausdrucks reduziert bzw. gesteigert werden sollten, veränderte sich die Aktivierung der Amygdala entsprechend.

Wie erwartet führte die Instruktion, die Reize kognitiv neu zu bewerten, im Vergleich zum Beibehalten von Emotionen unabhängig von der Regulationsrichtung zu einer stärkeren Aktivierung des dorsolateralen präfrontalen Kortex (dlPFC; rechter superiorer frontaler Gyrus). In Abbildung 4 ist zu sehen, dass die Verstärkung von Emotionen mit Aktivität im linken superioren, frontalen Gyrus assoziiert war (Abb. 4 A), während die Verringerung von Emotionen mit Aktivität im rechten superioren frontalen Gyrus assoziiert war (Abb. 4 B). Bei der Instruktion, die Emotionen herunter zu regulieren, beobachteten wir zusätzlich gesteigerte Aktivität im mittleren frontalen Gyrus (Abb. 4 C und D). Diese präfrontalen Hirnregionen zeigten sich auch in anderen Studien, in denen die Verstärkung und Verringerung von unangenehmen emotionalen Zuständen untersucht wurden (Eip-

## Amygdala Aktivität

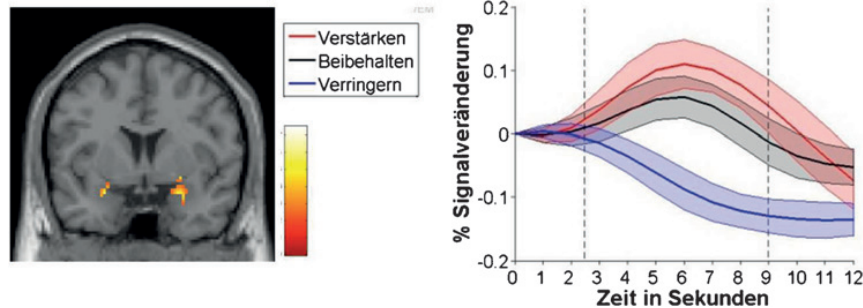


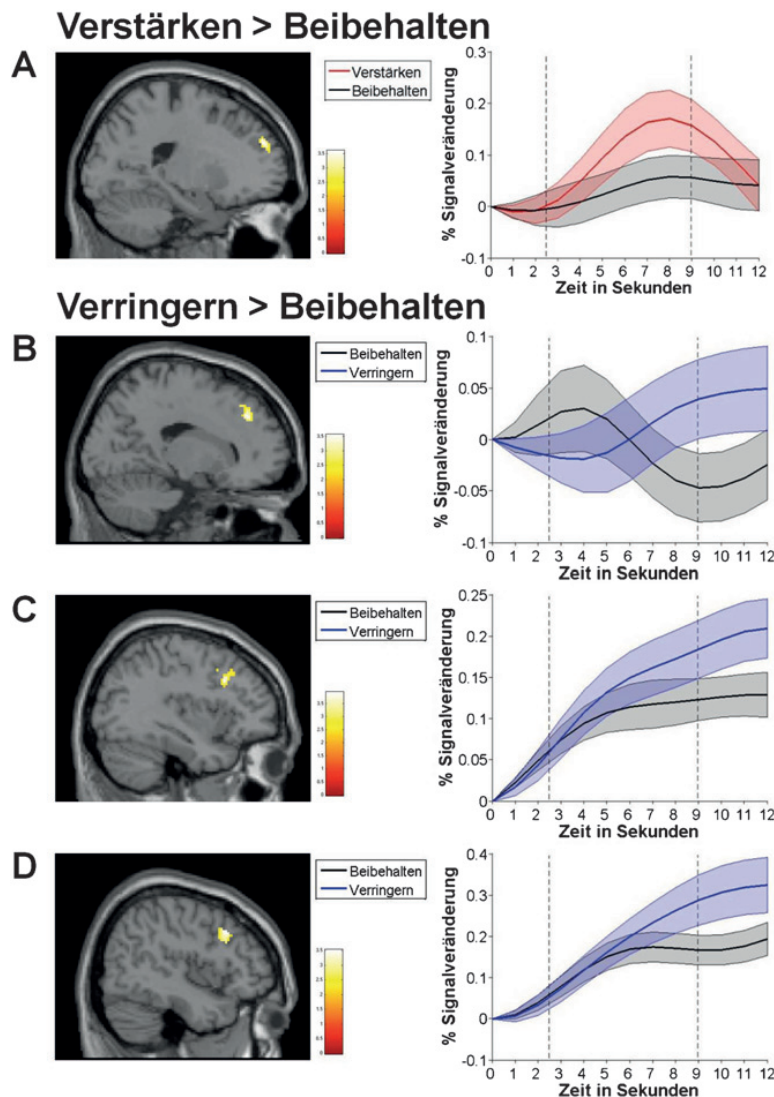
Abbildung 3. Aktivität in der Amygdala, die durch die Regulationsrichtung erklärt wird. Links sind die Hauptaktivierungen in der Amygdala (MNI:  $\pm 25, 4, -18$ ) abgebildet und rechts ist der Zeitverlauf der BOLD-Reaktion dargestellt.

pert et al. 2007, Ochsner et al. 2004). Traditionell wird der dlPFC mit Funktionen des Arbeitsgedächtnisses sowie mit kognitiver Kontrolle assoziiert (Gazzaniga, Ivry & Mangun, 2009). Außerdem ist diese Hirnregion direkt an der Repräsentation von Zielen beteiligt (Davidson, Jackson & Kalin, 2000). Eine Funktion des dlPFC könnte also darin bestehen, das eigene Verhalten (inklusive der eigenen Emotionalität) so zu steuern, wie es gemäß den externen situativen Anforderungen und den eigenen Zielen angemessen ist (vgl. Ochsner & Gross, 2004). Diese Annahme kann die Aktivierung des dlPFC sowohl bei der Verstärkung als auch bei der Verringerung von Emotionen erklären. Allerdings gibt es Hinweise, dass die Verringerung von Emotionen mit stärkerer Aktivität im rechten dlPFC einhergeht (Ochsner, Silvers & Buhle, 2012), was sich auch in unserer Studie zeigt (vgl. Abb. 4). Dies kann daran liegen, dass es schwieriger ist, Emotionen zu hemmen als sie zu steigern und daher mehr kognitive Kontrolle für die Reduktion notwendig ist (Ochsner et al., 2004). Allerdings gibt es bisher kaum Studien, in denen die Verstärkung von Emotionen untersucht wurde.

An dieser Stelle muss betont werden, dass sich diese während der Regulationsphase gefundenen Aktivierungsmuster nicht automatisch im Sinne eines kausalen Zusammenhangs interpretieren lassen. Um dies zu ermöglichen, müsste überprüft werden, ob die psychische Funktion – also die Fähigkeit zur Emotionsregulation – durch Schädigungen der entsprechenden dorsolateralen präfrontalen Areale spezifisch beeinträchtigt wäre. Dies ließe sich beispielsweise durch Studien an Patienten mit umschriebenen Läsionen in diesem Areal nachweisen oder dadurch, dass diese Struktur z. B. durch transkranielle Magnetstimulation kurzfristig in ihrer Funktion beeinträchtigt würde. Man würde dann eine entsprechende Beeinträchtigung der Emotionsregulation erwarten. Solche eher experimentell kausal angelegte Studien gibt es bisher jedoch noch nicht. Korrelative Studien existieren dagegen mehrere. Sie zeigen, dass die Verringerung der Amygdala Aktivität während der kognitiven Neubewertung unangenehmer Emotionen mit einer verstärkten

Aktivität im dorsomedialen und ventrolateralen präfrontalen Kortex einher geht (Johnstone, van Reekum, Urry, Kalin & Davidson, 2007; Urry et al., 2006). Dieser Zusammenhang scheint über die Aktivität im ventromedialen präfrontalen Kortex (vmPFC) vermittelt zu werden (Johnstone, van Reekum, Urry, Kalin & Davidson, 2007; Urry et al., 2006). Weitere Hinweise über die inhibitorische Wirkung des vmPFC auf die Amygdala stammen aus dem Bereich der Extinktionslernens von Furcht (Phelps, Delgado, Nearing & LeDoux, 2004). Die Verringerung der Furchtreaktion geht hier mit abnehmender Amygdala Aktivität und zunehmender vmPFC Aktivität einher (Phelps et al., 2004). Sowohl beim Menschen als auch bei Tieren scheint der vmPFC eine inhibitorische Wirkung auf die Amygdala-Aktivität und damit auf den Ausdruck unangenehmer Emotionen wie Furcht zu haben (Quirk & Beer, 2006). Im Kontext der kognitiven Neubewertung wird der vmPFC auch als Schnittstelle betrachtet, an der die Integration positiver und negativer Stimulus-Bewertungen in den aktuellen Kontext erfolgt (Roy, Shohamy & Wager, 2012). Außerdem wurde gezeigt, dass die Aktivität der Amygdala als Mediator zwischen der Abnahme des selbstberichteten Ausmaßes unangenehmer Emotionen und der Aktivität im ventrolateralen präfrontalen Kortex wirkt (Wager, Davidson, Hughes, Lindquist & Ochsner, 2008). Demnach wäre die Verringerung unangenehmen Erlebens eine Folge reduzierter Amygdala-Aktivität, die wiederum eine Folge erhöhter Aktivität im vmPFC wäre.

Bisherige Studien, in denen untersucht wurde, ob sich angenehme Emotionen leichter regulieren lassen als unangenehme, weisen übereinstimmend darauf hin, dass sowohl Überlappungen als auch Unterschiede bei den präfrontalen Aktivierungen zwischen den verschiedenen emotionalen Tönungen bestehen (Ohira et al., 2006; Kim & Hamann, 2007). Dies zeigt sich auch in unserer Studie, wobei insbesondere die Steigerung bzw. Reduktion der Aktivität der Amygdala unabhängig von dem hedonischen Gehalt der emotionalen Reize ist (vgl. Beauregard et al., 2001; Kim & Hamann, 2007).



*Abbildung 4. Präfrontale Aktivität A: Aktivität im linken superioren frontalen Gyrus während der Instruktion die Emotion zu verstärken (Verstärken minus Beibehalten) von Emotionen. Links sind die am stärksten aktivierten Voxel (MNI: -20, 52, 30), rechts ist der Zeitverlauf der BOLD-Reaktion in diesem Cluster abgebildet. Teil B bis D zeigt die Aktivierungen präfrontaler Areale bei der Instruktion die Intensität der Emotionen zu verringern. B: Links: Cluster der am stärksten aktivierten Voxel im rechten superioren frontalen Gyrus (MNI: 18, 38, 38); Rechts: Zeitverlauf der BOLD Reaktion in dieser Region. C Links: Aktivierung im linken mittleren frontalen Gyrus (MNI: -36, 18, 34) Rechts: Zeitverlauf der BOLD Reaktion in dieser Region. D: Aktivierung im rechten mittleren frontalen Gyrus (MNI: 46, 20, 38) und Zeitverlauf der BOLD Reaktion in dieser Region (rechts).*

Die bisherigen Studien zur Emotionsregulation sprechen dafür, dass Emotionsregulation kein distinkter Vorgang ist, sondern auf abgrenzbaren Prozessen basiert. Diese sind zu unterschiedlichen Zeitpunkten bedeutsam und werden mit unterschiedlichen Hirnregionen assoziiert. So argumentiert beispielsweise Kalisch (2009), ausgehend von den Bewertungstheorien von Emotionen (vgl. Scherer, 2001), dass kognitive Neubewertung kein einheitliches Ereignis ist, sondern ein zeitlich ausgedehnter und dynamischer Prozess, welcher sich in einem kontinuierlichen, linearen Anstieg der Hirnaktivität im Zusammenhang mit kognitiver Neubewertung abbildet. In einer Metaanalyse zur kognitiven Neubewertung (Kalisch, 2009) fand sich eine Verschiebung der neurobiologischen Aktivität mit zunehmender Länge der Regulationsphase von Aktivierungen im linken frontalen Kortex

zum rechten frontalen Kortex, sowie von posterioren zu anterioren Regionen. Diese Befunde deuten an, dass mehrere neuronale Netze im Sinne einer sich ausbreitenden Erregung sequentiell im frontalen Kortex aktiviert werden, wenn Menschen versuchen, ihre Emotionen entsprechend der situativen Anforderungen und der gespeicherten Handlungsziele zu regulieren. Unterschiedliche Zeitverläufe könnten auch besonders bei differierenden Regulationsstrategien eine Rolle spielen. So gibt es Hinweise dafür, dass die kognitive Neubewertung von Ekel mit frühen präfrontalen Aktivierungen und später reduzierter Aktivität in der Amygdala und der Inselrinde einhergeht, wohingegen die Emotionsunterdrückung sowohl mit später präfrontaler als auch mit später Aktivität in Amygdala und Inselrinde assoziiert ist, also weniger erfolgreich zu sein scheint (Goldin et al., 2008). In unserer

Studie finden wir verstärkte präfrontale Aktivität bei der kognitiven Neubewertung im Vergleich mit der Reaktionsmodulation, allerdings sind beide Strategien gleichermaßen mit einer Reduktion der Amygdala-Aktivität assoziiert.

Hierbei ist zu beachten, dass die Studien zur Emotionsregulation sich in vielen Faktoren unterscheiden. Neben Variationen der Zeitdauer, die für die Regulation zur Verfügung steht, oder dem Zeitpunkt, zu dem die Regulationsinstruktion dargeboten wird, werden auch unterschiedliche emotionsauslösende Reize (z. B. IAPS-Bilder oder Filme) verwendet. Auch die Instruktionen für die Regulationsstrategien variieren zwischen den Studien. Einheitliche Methoden zur Auswertung der Hirnaktivität fehlen ebenfalls. Es gibt also sowohl methodische Gründe als auch inhärente Eigenschaften des Konstrukts, die es zum aktuellen Zeitpunkt schwierig machen, ein in allen Facetten einheitliches Bild der neurobiologischen Grundlagen der Emotionsregulation zu entwickeln.

Unabhängig von der Valenz sowie von der verwendeten Regulationsstrategie lässt sich allerdings zusammenfassen, dass ein emotional bedeutsamer Reiz oder ein solches Ereignis zunächst von der Amygdala registriert wird. Die Amygdala vermittelt dann die emotionale Reaktion (z. B. Veränderungen in Herzraten, Verhalten und Vigilanz) über entsprechende Verbindungen zu Hypothalamus- und Hirnstammkernen. Diese Veränderungen in der autonomen Erregung werden auch von der Inselrinde registriert. Aus dieser Information wird in Zusammenhang mit der Bewertung der Situation vermutlich die subjektive Gefühlskomponente einer Emotion konstruiert. Dieser Emotionsgenerierungsprozess kann dann zusätzlich von präfrontalen Regionen (besonders dlPFC und vmPFC) in Abhängigkeit von situativen Anforderungen und persönlichen Handlungszielen verstärkt oder gehemmt werden.

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# Study 1

## **Resting state high-frequency heart rate variability is associated with neural activity during explicit emotion regulation**

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In preparation

Author contributions:

AH, JW, and ES designed the study, ES did the laboratory assessment, ES pre-processed and analyzed the data under supervision of JW, FG and JK. All authors contributed to the interpretation of the data and wrote the manuscript (first draft provided by ES).



**Resting state high-frequency heart rate variability is associated with neural  
activity during explicit emotion regulation**

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Running head: Vagal Activity and Neural Emotion Regulation

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## Abstract

Resting state high-frequency heart rate variability (HF-HRV) is related to difficulties in emotion regulation (ER). The prefrontal cortex (PFC) provides inhibitory control over the amygdala during ER. Previous studies linked HF-HRV with activity in the ventromedial PFC (vmPFC) during *implicit* ER. To date no study examined the relation between HF-HRV and brain activity during *explicit* ER. HF-HRV was measured during a 7 minutes baseline at T1 2-5 days preceding T2. At T2 24 participants (50% female,  $M_{\text{age}}=24.6$  years) viewed neutral or emotional pictures of pleasant or unpleasant valence and were instructed to intensify or to reduce their present emotion using two ER strategies (*reappraisal* and *response modulation*) or to passively view the picture. Participants rated their emotional state on two dimensions of valence and arousal after ER. Whole-brain fMRI data were collected using a 1.5-T-scanner. We observed interactions between resting state HF-HRV and brain activation in the PFC and the amygdala during ER of unpleasant emotions. Groups based on HF-HRV showed significant differences in the modulation of amygdala activity as a function of ER strategy. In participants with *high* HF-HRV amygdala activity was modulated only when using *reappraisal* and for *low* HF-HRV participants only when using *response modulation*. Similar, dorsomedial PFC (dmPFC) activity in *high* HF-HRV participants was increased when using *reappraisal* and in *low* HF-HRV participants when using *response modulation* to regulate unpleasant emotions. These results suggest that individuals with *low* HF-HRV might have difficulties in recruiting prefrontal brain areas necessary for the modulation of amygdala activity during explicit ER.

**Keywords:** prefrontal cortex, amygdala, heart rate variability, emotion regulation

## Introduction

Emotion regulation (ER) can be defined as “*the evocation of thoughts or behaviors that influence which emotions people have, when people have them, and how people experience or express these emotions*” (Richards & Gross, 2000, p. 411). A host of brain imaging studies suggest that increased activation of the prefrontal cortex (PFC) is essential for ER (Beauregard, Lévesque, & Bourgouin, 2001; Ochsner & Gross, 2005; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008). The PFC is theorized to have an inhibitory top down control over the amygdala during *explicit* (intentional) ER (Ochsner, Bunge, Gross, & Gabrieli, 2002; Urry et al., 2006).

Resting state high-frequency heart rate variability (HF-HRV), reflecting the potential for fast parasympathetic modulation of autonomic control of the heart, is inversely related to affective instability in daily life (Koval et al., 2013), and inversely correlated with self-reports on difficulties in ER (Beauchaine, 2015; Borna, Ott, & Nandrino, 2014; Williams et al., 2015). Recent research suggests a relationship between brain activity and HF-HRV, as higher resting state HF-HRV is associated with stronger functional connectivity between the amygdala and the medial PFC (mPFC) across younger and older adults (Sakaki et al., 2016).

Importantly, in a series of studies on *implicit* (non-intentional) ER we have recently shown that 1) activity in ER related areas of the brain was positively correlated with coincident HF-HRV during processing stimuli with its emotional significance in the attentional background (Lane et al., 2013); 2) that these relationships were absent in depression but increased and were similar to non-depressed controls after 12 week treatment with sertraline (Smith, Allen, Thayer, Fort, & Lane, 2014); and 3) that mPFC connectivity with the pons was negatively associated with depressive symptoms and positivity associated with coincident HF-HRV when processing emotional stimuli with a non-emotional focus (Smith, Allen,

Thayer, & Lane, 2015). These studies suggest that HF-HRV and brain activity co-vary during *implicit* ER and that individual differences exist such that these associations are reduced or absent in persons with *low* HF-HRV such as depressed patients (Kemp et al., 2010; Koenig, Kemp, Beauchaine, Thayer, & Kaess, 2016).

While previous neuroimaging studies (e.g. Lane et al., 2013) demonstrated activity in the ventromedial PFC (vmPFC) during *implicit* (non-intentional) ER to be related to resting state HF-HRV, the majority of neuroimaging studies on ER focused on *explicit* ER (i.e., intentional changes in affective state). However, surprisingly to date no study has examined the relationship between individual differences in resting HRV and brain activity during *explicit* ER.

Thus, the present study aimed to investigate the neural concomitants of *explicit* ER as a function of resting state HF-HRV. Participants were trained in two ER strategies: *reappraisal* and *response modulation* and the neural activation during up- and down-regulation of emotions were measured. Resting state HF-HRV was used to stratify participants into two groups. Based on previous findings it was hypothesized that individuals with *high* resting state HF-HRV would exhibit differentiated activation of prefrontal brain regions and the amygdala according to the ER direction and that *low* resting state HF-HRV would be related to less involvement of PFC structures and less modulation of the activation of the amygdala.

## **Materials and Methods**

### *Participants and General Procedures*

Twenty-seven students participated in this investigation. Participants were selected if they were right-handed, had no current or prior mental disorders, and did not meet any MRI exclusion criteria, including metal in the body, claustrophobia, or pregnancy. Two participants did not complete the study due to schedule difficulties

and one examination was discontinued due to technical problems. The final sample ( $n = 24$ ) consisted of 12 female and 12 male participants, with a mean age of 24.6 years (range: 21 to 33). Participants received course credits or were paid an expense allowance of seven euro. All participants gave written informed consent to the experiment approved by the University of Greifswald ethics committee.

The investigation consisted of two parts: (1) a training session in the psychophysiological laboratory of the Institute of Psychology, two to five days prior to the experiment, and (2) the fMRI-experiment in the university clinic. During the training session participants practiced the two ER strategies and got familiar with the design of the study. Furthermore, their HF-HRV was measured for 7 minutes in silence with a link belt, the Polar F5 Heart Rate Monitor Watch (Polar Electro Oy, Finland).

The fMRI-Session started with an introduction of the MRI-scanner and a medical check for participation by the clinic staff. The instructions for the ER strategies were repeated for each regulation direction and participants were asked to view all pictures attentively the whole time and not to close their eyes or move their head away from the picture. Pictures were projected on a tilted mirror mounted on the head coil.

### *Stimulus Material*

Based on normative valence and arousal ratings and the general content two comparable sets of 36 pleasant and 36 unpleasant pictures were selected from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2005). Arousal ratings were balanced for pleasant ( $M = 5.60$ ,  $SD = 0.99$ ) and unpleasant ( $M = 5.83$ ,  $SD = 0.69$ ) stimuli. Two comparable sets of 12 neutral pictures were used as reference stimuli. For each participant, the two picture sets were randomly assigned to

the two ER strategies and were presented in six pseudo-randomized orders across participants.<sup>1</sup>

To standardize the regulation of emotions, specific instructions were given for each strategy. Generally, participants were instructed not to replace one emotion by another but to intensify (*increase*) or to reduce (*decrease*) their present emotion or to just view the picture passively (*maintain*; cf. Ochsner and Gross, 2005). Participants were instructed to apply two ER strategies: *Reappraisal* and *response modulation*. *Reappraisal* involved the cognitive variation of the dimension distance-intimacy. To increase the emotion participants were instructed to reduce the distance to the depicted content by imagining to be either personally involved in the scene or indirectly via persons to whom they have a close relationship (e.g., friends, family, etc.). To decrease the emotion, distance was enhanced by imagining the picture as a simulation or by imagining being a casual bystander. *Response modulation* focused on changes of respiration, body tension and facial expressions, which were intensified to increase and reduced to decrease the emotion. Participants were also instructed to modulate the visibility of their emotions according to the regulation goal. In the increase condition a possible spectator should recognize the experienced emotion, whereas in the decrease condition a possible spectator should not be able to recognize which emotion is experienced.

Participants rated their emotional state on the two dimensions of valence and arousal after regulating their emotions using the Self-Assessment Manikin (SAM; Bradley & Lang, 1994): valence ratings ranged from pleasant to unpleasant (range 1-5); arousal ratings ranged from calm to excited (range 1-5). Since these ratings were recorded after each ER period, they can be considered as indicators of regulation success.

### *Experimental Paradigm*

The experimental paradigm was a modified version from Eippert and co-workers (Eippert et al., 2007). It consisted of two experimental runs, one for each ER strategy. Every run was composed of 84 trials, 12 for each condition. The seven conditions reflected the seven regulation directions: pleasant-increase, pleasant-maintain, pleasant-decrease, neutral-maintain, unpleasant-increase, unpleasant-maintain and unpleasant-decrease. All trials consisted of the following phases: induction, instruction, regulation and rating. Each trial began with the presentation of a picture for 2.5 s, which participants were instructed to view and to allow their emotional reactions to occur (induction phase). Then the instruction – equal sign (*maintain*), arrow up (*increase*), or arrow down (*decrease*) – appeared in the centre of the picture, signaling the participants to regulate their emotions according to the practiced ER strategies during the training session. After 500 ms the instruction disappeared and the following 6 s were given for regulation with the picture still present. After the regulation phase SAM valence and arousal rating scales were presented for 3 s each and participants rated their current emotional experience. During an inter-trial-interval (8-10 s) a fixation cross was presented that signaled the participants to rest.

### *fMRI-Data Acquisition*

Whole-brain fMRI data were collected using a 1.5 T scanner Magnetom Symphony system (Siemens) equipped with an 8-channel head coil. During the two regulation runs 506 functional T2\*-weighted images were acquired in transversal direction using echo-planar imaging (EPI) with a repetition time (TR) of 4 s, Field of view (FoV)= 192 mm, matrix= 128 x 128, flip angle= 90°, echo time (TE)= 38 ms). Each functional volume comprised 33 slices (voxel size: 3 x 1.5 x 1.5 mm). Between

the two functional runs, a high-resolution anatomical T1-weighted scan was acquired with a TR of 11 ms (FoV= 256 mm, matrix= 256 x 256, TE= 5.2 ms, voxel size: 1 x 1 x 1 mm).

### *Data Analysis*

The central 5 min of the recorded 7 min HR data were analyzed with HRV Analysis (Niskanen, Tarvainen, Ranta-aho, & Karjalainen, 2004). The root mean square of successive differences (RMSSD) is thought to represent vagally mediated HRV and was used as time-domain measure of HF-HRV (Task Force Guidelines, 1996). The RMSSD was extracted for each participant and further included in analysis with SPSS (SPSS IBM Statistics 22). High and low HF-HRV groups were separated on basis of the median split ( $MD = 56.05$ ; low HF-HRV  $M = 37.49$ ; high HF-HRV  $M = 79.08$ ).

Valence and arousal ratings obtained after the regulation process were analyzed with a repeated measures analysis of variance (ANOVA) with the within-factors Strategy (*reappraisal* vs. *response modulation*), Valence (*pleasant* vs. *unpleasant*), and Direction (*increase* vs. *maintain* vs. *decrease*), and the between-factor HF-HRV (*low* vs. *high*). All data were analyzed with SPSS (SPSS IBM Statistics 22). All results reported met a significance level of  $p < .05$ , unless otherwise noted. Partial eta-squared ( $\eta p$ ) was used as measure of effect size, indicating the proportion of the total variance in a dependent variable explained by an independent variable while the effects of other independent variables and interactions are partialled out.

MRI-data pre-processing and statistical data analysis were performed with Statistical Parametric Mapping software (SPM8, Wellcome Department of Imaging

Neuroscience, London, UK). The functional images of each subject were acquisition time corrected to the middle slice, realigned, co-registered to the anatomical image, segmented, and spatially normalized to a standard template of the Montreal Neurological Institute (MNI) and smoothed (FWHM 8 mm).

During first level analyses, for each participant a general linear model, as implemented in SPM8, was applied to the time-course of each voxel. The induction and regulation phase were modeled together using a boxcar function with a length of 9 s convolved with the hemodynamic responses function. The six movement parameters estimated during the realignment procedure were introduced as covariates into the model to control for variance caused by head movements. The resulting beta images were further analyzed on the second level in a full factorial model with the factors Strategy (reappraisal vs. response modulation), Valence (pleasant vs. unpleasant), and Direction (increase vs. maintain vs. decrease).<sup>2</sup> The amygdala response to the experimental manipulation was quantified by means of the main effect of regulation direction. The prefrontal regions involved in ER were identified by means of the contrast ‘regulate (increase and decrease) vs. maintain’.

The time course of amygdala and prefrontal clusters exceeding a significance threshold of  $p < .001$  (uncorrected) and an extend threshold of  $k = 5$  were extracted using rfxplot (Gläscher, 2009) with spheres of a 3 mm radius centered around the individual peak activation within that cluster. Extracted scores were averaged for the 6 seconds of instructed emotion regulation and analyzed with SPSS (SPSS IBM Statistics 22) as described for valence and arousal ratings.

## Results

### *Valence Ratings*

As indicated by a significant 4-way interaction (Strategy x Valence x Direction x HF-HRV:  $F_{(2,44)}: 4.77, p = .013, \eta^2_p = .18$ ), the valence ratings of the participants current emotional state when using different ER strategies were influenced by HF-HRV only when down-regulating unpleasant emotions. Compared to the corresponding maintain condition, participants with high HF-HRV reported less unpleasant feelings after down-regulating their emotions using reappraisal ( $t_{(11)} = 5.22, p < .001$  for reappraisal;  $t_{(11)} = 2.51$ , ns after bonferroni correction for response modulation). In contrast, participants with low HF-HRV reported a greater subjective reduction in unpleasantness when using response modulation ( $t_{(11)} = 3.28, p = .007$  for response modulation;  $t_{(11)} = 2.25$ , ns after bonferroni correction for reappraisal; Strategy x Direction x HRV (*unpleasant*):  $F_{(2,44)} = 5.49, p = .007, \eta p = .20$ ; see *Figure 1*). No such effect of HF-HRV was found for valence ratings after regulating emotions evoked by pleasant pictures (Strategy x Direction x HRV (*pleasant*):  $F < 1$ ).

### *Amygdala*

Whole-brain analysis revealed a main effect of ER direction in clusters in both the right (MNI:  $x = 24, y = 4, z = -16; F = 7.36, p_{uncorr} < .001, k_E = 5$ ) and the left (MNI:  $x = -24, y = 2, z = -18; F = 12.51, p_{uncorr} < .001, k_E = 15$ ) amygdala.

As for valence ratings, resting HF-HRV levels influenced right amygdala responses as a function of valence and regulation strategy (Strategy x Valence x Direction x HF-HRV:  $F_{(2,44)}: 3.11, p = .06, \eta p = .12$ ). That is, the differentiation, between increasing and decreasing their negative states was more pronounced for high HF-HRV participants when using reappraisal (increase > decrease;  $t_{(11)} = 3.95, p = .002$ ) but not when using response modulation ( $t_{(11)} = .21, ns$ ) and for low HF-HRV

participants when using response modulation ( $t_{(11)} = 4.57, p = .001$ ) but not when using reappraisal ( $t_{(11)} = .95, ns$ ). No effects of resting HF-HRV were found on right amygdala response during the regulation of emotions evoked by pleasant pictures (Direction x HF-HRV:  $F_{(2,44)} = 1.58, n.s.$ ; Strategy x Direction x HF-HRV:  $F < 1$ ).

Resting HF-HRV did not affect left amygdala responses during emotion regulation (Direction x HF-HRV:  $F < 1$ ), neither as a function of stimulus valence (Valence x Direction x HF-HRV:  $F_{(2,44)} = 2.29, ns$ ) nor as a function of regulation strategy (Strategy x Direction x HF-HRV:  $F_{(2,44)} = 1.01, ns$ ) or both (Strategy x Valence x Direction x HF-HRV:  $F < 1$ ).

### *Prefrontal Cortex*

Whole-brain analysis revealed five clusters in the dorsolateral PFC (dlPFC) and one cluster in the dorsomedial PFC (dmPFC) showing a more pronounced response to conditions in which participants were instructed to regulate their emotions (Regulate > Maintain; see *Table 1*). Since an influence on resting HRV on amygdala activity was only found during regulating emotions evoked by unpleasant pictures, the subsequent analyses of prefrontal regions was conducted for the negative valence category only. Resting HF-HRV did not affect responses during ER in the five dlPFC clusters. In contrast, unlike valence ratings and right amygdala responses, responses in the dorsomedial cluster (MNI:  $x = 12, y = 46, z = 36$ ) during regulating emotions evoked by unpleasant pictures were influenced by resting HF-HRV levels as a function of the used regulation strategy (Strategy x Direction x HF-HRV:  $F_{(2,44)} = 3.59, p = .036, \eta^2_p = .14$ ; see *Figure 2*). Compared to the corresponding maintain condition, participants with high HF-HRV showed enhanced dmPFC activity while up-regulating unpleasant emotions using reappraisal ( $t_{(11)} = 3.44, p = .005$ ) but not when using response modulation ( $t_{(11)} = 1.53, ns$ ), whereas participants with low HF-HRV

showed no significant difference during reappraisal ( $t_{(11)} = 1.66$ , *ns*) or response modulation ( $t_{(11)} = 1.78$ , *ns*). In contrast, low HF-HRV participants showed more pronounced dmPFC activity while down-regulating unpleasant emotions using response modulation ( $t_{(11)} = 2.97$ ,  $p = .013$ ) but not while using reappraisal ( $t_{(11)} = .39$ , *ns*), whereas participants with high HF-HRV showed no significant difference during response modulation ( $t_{(11)} = -.79$ , *ns*) or reappraisal ( $t_{(11)} = 1.44$ , *ns*). In direct comparison, low HF-HRV participants showed more pronounced dmPFC activity while down-regulating unpleasant emotions using response modulation compared to high HF-HRV participants ( $t_{(22)} = 3.13$ ,  $p = .005$ ). In sum, when regulating unpleasant emotions (mean of dorsomedial activity while up- and down-regulating) compared to maintaining emotions, high HF-HRV participants showed significantly increased dmPFC activity when using reappraisal ( $t_{(11)} = 2.38$ ,  $p = .037$ ) but not when using response modulation ( $t_{(11)} = .70$ , *ns*). In contrast, participants with low HF-HRV showed significantly increased dmPFC activity when using response modulation ( $t_{(11)} = 2.56$ ,  $p = .026$ ) but not when using reappraisal ( $t_{(11)} = 1.10$ , *ns*) as ER strategy.

## Discussion

This is the first study to combine functional imaging data of the *explicit* ER process and habitual resting state HF-HRV data. We observed a differentiated modulation of the activation of the dmPFC and the amygdala according to the participants' HF-HRV. Thus these results further support recent findings on the relationship between resting state amygdala-PFC functional connectivity and HF-HRV, and increase our understanding of the neural concomitants of HF-HRV and its role in ER.

We observed that in participants with *high* HF-HRV right amygdala activity was modulated according to the regulation direction (i.e., enhanced when instructed to

*increase* and diminished when instructed to *decrease*) only when *reappraisal* was used to regulate unpleasant emotions. In contrast, in participants with *low* HF-HRV the same modulation of amygdala activity was observed when *response modulation* was used to regulate unpleasant emotions. Similarly, only in participants with *high* HF-HRV right dmPFC activity was increased when using *reappraisal* to regulate unpleasant emotions whereas participants with *low* HF-HRV showed increased activation of the right dmPFC using *response modulation* to regulate unpleasant emotions.

These findings add to the existing findings on the neural concomitants of HF-HRV during *implicit* ER (e.g., Lane et al., 2013), and provide further support for the *Neurovisceral Integration Model* (Thayer & Lane, 2000), which proposes that individuals with high resting state HF-HRV are better able to inhibit prepotent emotional responses in the service of more desirable and appropriate ones in accordance with contextual factors. In line with this view, Geisler and colleagues (2010) have shown that HF-HRV is positively associated with subjective well-being, and that this relationship is mediated by the habitual use of executive (i.e., conscious cognitive) ER strategies such as *reappraisal*. Therefore, our data support the findings by Geisler and colleagues (2010) showing that *high* HF-HRV might be beneficial for the *explicit* cognitive regulation of emotions.

Most interestingly, participants with *low* HF-HRV showed modulated activation of the right amygdala during the use of *response modulation*. *Response modulation* focuses on changes of respiration, body tension and facial expressions that do not rely on executive (prefrontal) recruitment to the same degree as *reappraisal*, which involves cognitive variation of the dimension distance-intimacy to the depicted content. Differences in the executive recruitment between those with *low* and *high* HF-HRV might explain modulated activation of the amygdala only during

the use of *response modulation* in those with *low* HF-HRV, while those with *high* HF-HRV showed modulated activation of the amygdala during *reappraisal*.

Indeed, our data show that the dmPFC seems to play an important role in the top-down modulation of the amygdala activation. Whereas only participants with *high* HF-HRV showed enhanced activation of the right dmPFC using *reappraisal* to regulate unpleasant emotions and enhanced modulated activation of the amygdala; participants with *low* HF-HRV showed enhanced activation of the right dmPFC using *response modulation* to regulate unpleasant emotions and enhanced modulated activation of the amygdala. Taken together these findings suggest, that those with *low* HF-HRV have particular difficulties in conscious, cognitive ER (i.e. *reappraisal*), that involve the recruitment of executive brain areas necessary for the top-down modulation of the amygdala. These findings support the hypothesis that greater resting HF-HRV may reflect the efficiency of the prefrontal cortex to regulate amygdala activity in the service of ER.

In line with these observations, we have recently shown that *higher* HF-HRV is associated with stronger resting state functional connectivity between the amygdala and the mPFC (Sakaki et al., 2016). Whereas this association was present independent of age, we also found age-related differences in the amygdala's functional connectivity associated with HF-HRV. Compared to older adults, we found that the functional connectivity between the amygdala and the ventrolateral PFC (vlPFC) was more strongly correlated with HRV in younger adults (Sakaki et al., 2016). In line with these findings it has previously been shown that during (*implicit*) ER older and younger adults spontaneously recruit the mPFC (Nashiro, Sakaki, & Mather, 2012), while in addition to the mPFC younger adults also recruit the vlPFC during (*explicit*) ER (Winecoff, LaBar, Madden, Cabeza, & Huettel, 2011). Clearly, future studies

addressing age related differences in the neural concomitants of *implicit* and *explicit* ER as a function of resting state HF-HRV are needed.

Existing research implicates dlPFC regions in voluntary ER and vmPFC regions (including ACC) in automatic – more habitual – ER (Phillips, Ladouceur, & Drevets, 2008; Silvers, Wager, Weber, & Ochsner, 2015). Therefore, it is suggested that *explicit* ER involves greater lateral PFC recruitment (Gyurak, Gross, & Etkin, 2011), a brain region that shows thinning with increasing age (Fjell et al., 2009). Greater connectivity between vmPFC and amygdala has been shown in older adults even when not told to use *explicit* ER, suggesting that *explicit* ER strategies have become habitual and automatic (Ochsner, Silvers, & Buhle, 2012). Here we have shown in line with a large body of research (Ochsner et al., 2012), that *explicit* ER leads to enhanced activation of the dlPFC. The lack of association of HF-HRV with activity of the dlPFC suggests a particular association with HF-HRV and *implicit* – automatic – ER. However, we found HF-HRV related to activation of the dmPFC during *explicit* ER. As noted above, this finding suggests that explicit ER strategies that require enhanced recruitment of PFC regions are related to HF-HRV. In particular, the present results show that activation of the right dmPFC significantly varied between participants with *low* and *high* HF-HRV according to the ER direction and strategy. Future research is needed to fully explicate the associations of HRV with both *implicit* and *explicit* ER.

Differences might also arise as a result of the use of different *explicit* ER strategies. Most fMRI studies on *explicit* ER focused on the down-regulation of unpleasant emotions with *reappraisal* (i.e., the cognitive change of the meaning of a picture; e.g. Ochsner et al., 2002; Eippert et al., 2007; Goldin, McRae, Ramel, & Gross, 2008), or *suppression* (i.e., the inhibition of an ongoing emotion-expressive behavior; e.g. Gross, 1998b; Goldin et al., 2008). While our implementation of

*reappraisal* is consistent with these studies, our implementation of *response modulation* is much broader than that of *suppression*, since we instructed participants to suppress or enhance their facial expressions or to influence their physiological responses by increasing or decreasing their respiration or their muscle tension. Particularly the regulation of respiration might account for the effectiveness of *response modulation* in participants with *low* HF-HRV. Respiration patterns have been shown to reflect the general dimensions of emotional response (Boiten, Frijda, & Wientjes, 1994), in particular the arousal dimension of self-reported emotions (Nykliček, Thayer, & Van Doornen, 1997). Previous studies comparing the two ER strategies of *physiological suppression* and *expressive suppression* (Dan-Glauser & Gross, 2011) found that both ER strategies, although targeting different responses, have very similar effects. Therefore, it might be possible that *response modulation* in our study was a multidimensional *explicit* ER strategy, which encompassed the manipulation of one's facial expression, breathing frequency, and body tension. Future research is needed to clarify whether participants with *low* HF-HRV are indeed more effective in non-cognitive emotion regulation strategies focusing on manipulations of the breathing frequency.

## Summary

In conclusion, our results replicate and extend findings from neuroimaging studies on ER and significantly add to the literature by showing that individual differences in resting state HF-HRV predict different patterns of neural activity during *explicit* ER. In line with the process model of ER (Gross, 1998a), we observed enhanced activation of prefrontal brain structures associated with emotional control whereas activation of the amygdala was modulated according to the ER direction. Our

data provide first evidence for neural differences during explicit ER using different ER strategies as a function of resting state HF-HRV. Participants with *high* HF-HRV only show modulated activation of the right amygdala during the use of *reappraisal* whereas participants with *low* HF-HRV show modulate activation of the right amygdala only during the use of *response modulation*. Further, we found increased activation of the dmPFC in participants with *high* HF-HRV when regulating unpleasant emotions with reappraisal and in participants with *low* HF-HRV when regulating unpleasant emotions. Future studies need to address age related differences in the neural concomitants of HF-HRV during *explicit* ER and should aim to replicate these findings in samples with difficulties in ER (i.e., depressed patients). Adding to existing findings on the neural concomitants of HF-HRV during *implicit* ER, the present findings support the *Neurovisceral Integration Model* (Thayer and Lane, 2000), suggesting that higher HF-HRV is associated with neural mechanisms that support successful ER.

### **Footnotes**

1. The following randomized orders were generated: Order one started with a pleasant picture and the instruction to increase, order two started with a pleasant picture and the instruction to just view passively, order three started with a pleasant picture and the instruction to decrease the emotion, order four started with a unpleasant picture and the instruction to just view passively, order five started with a unpleasant picture and the instruction to decrease the appearing emotion and order six started with a unpleasant picture and the instruction to increase the emotion.
2. The overall results of this analysis are reported in Steinfurth, Wendt, & Hamm (2013).

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**Table 1.** Prefrontal clusters showing more pronounced activity during regulation conditions (increasing and decreasing emotions) compared to maintain conditions

No	Region	Side	MNI-coordinates			$k_E$	t-score*
			x	y	z		
1.	dorsolateral	L	-20	50	30	11	3.80
2.		L	-26	52	24	16	3.68
3.		L	-56	22	8	5	3.42
4.		R	20	38	36	27	3.74
5.		R	20	24	18	5	3.53
1.	dorsomedial	R	12	46	36	8	3.26

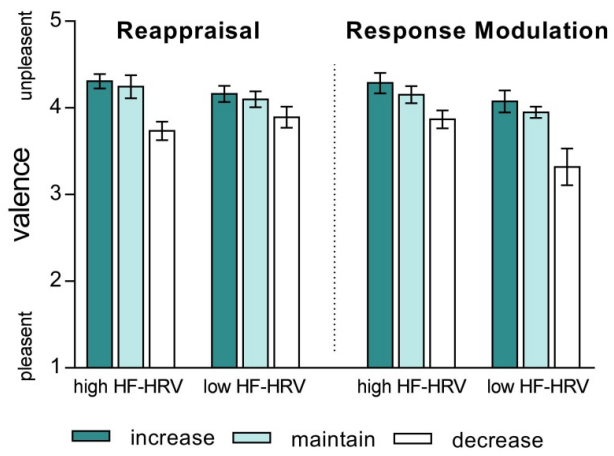
\*  $p_{\text{uncorr}} < .001$

## Figure Captions

**Figure 1.** Valence ratings of the current emotional state after regulating emotions evoked by unpleasant pictures using either reappraisal (left) or response modulation (right) in participants with high and low resting state high-frequency heart rate variability (HF-HRV). Bars represent group means with standard errors.

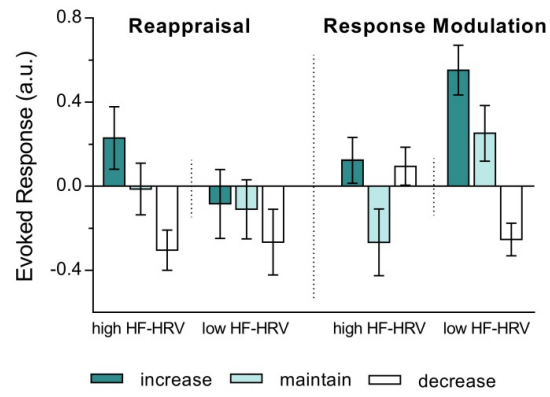
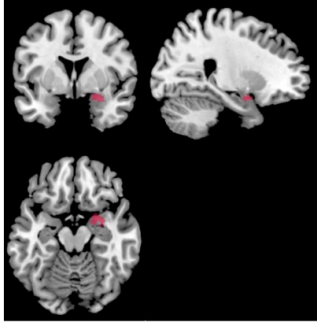
**Figure 2.** BOLD activation during the regulation of emotions evoked by unpleasant pictures using either reappraisal or response modulation in participants with high and low resting state high-frequency heart rate variability (HF-HRV). On the left side is the BOLD activity at  $p_{\text{uncorr}} = .001$ ,  $k=5$ , overlayed on a standard template (ch2better.nii.gz) using MRIcron ([www.cabiatl.com/mricro/mricron](http://www.cabiatl.com/mricro/mricron)). On the right side is the extracted data (individual spheres with a radius of 3 mm). Bars represent group means (arbitrary units) with standard errors. A: Right amygdala activation ( $y = 2$ ). B: Right dorsomedial prefrontal cortex (dmPFC) activation (MNI:  $x = 10$  to  $12$ ,  $y = 44$  to  $46$ ,  $z = 36$  to  $38$ ).

**Figure 1**

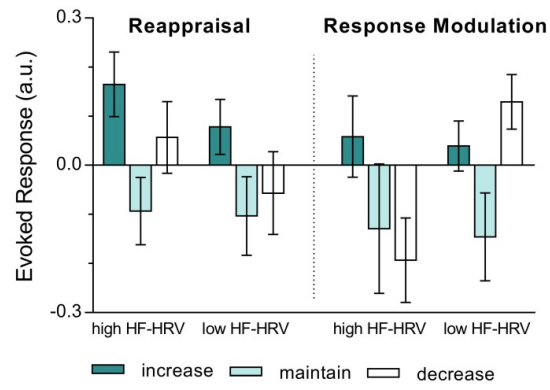
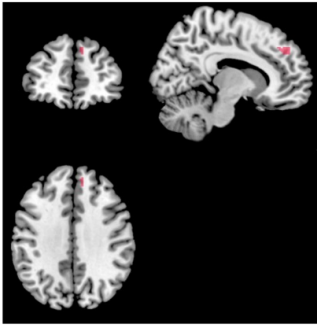


**Figure 2**

**A. Right Amygdala**



**B. Right dorsomedial PFC**





# Study 2

## **Young and old pavlovian fear memories can be modified with extinction training during reconsolidation in humans**

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Author contributions:

EP, RH, RC, CR, and ES designed the study, JK and ES did the laboratory assessment, ES preprocessed and analyzed the data with assistance of CR. All authors contributed to the interpretation of the data, ES and EP wrote the manuscript (first draft provided by ES).



## Brief Communication

# Young and old Pavlovian fear memories can be modified with extinction training during reconsolidation in humans

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Extinction training during reconsolidation has been shown to persistently diminish conditioned fear responses across species. We investigated in humans if older fear memories can benefit similarly. Using a Pavlovian fear conditioning paradigm we compared standard extinction and extinction after memory reactivation 1 d or 7 d following acquisition. Participants who underwent extinction during reconsolidation showed no evidence of fear recovery, whereas fear responses returned in participants who underwent standard extinction. We observed this effect in young and old fear memories. Extending the beneficial use of reconsolidation to older fear memories in humans is promising for therapeutic applications.

[Supplemental material is available for this article.]

Learning to predict threat from cues in the environment is adaptive. In order to remain adaptive, however, the memory of the association between a neutral cue and a threat cue, as well as the elicited fear response or defensive behavior, needs to be flexibly modified as situations change. The standard approach to modify fear is extinction or exposure training in which a new, safe association is learned, leading to a gradually diminished fear expression. With extinction, however, fear might return because the original fear memory is not significantly altered and must be inhibited to express the new extinction memory (Bouton 2004). It has been suggested that the inability to consistently inhibit fear memories following extinction or exposure may be a factor in the maladaptive expression of fear in anxiety, trauma, or stress-related disorders, such as post-traumatic stress disorder (PTSD) (Rauch et al. 2006). The potentially temporary nature of extinction or exposure training led to the search for strategies to more persistently alter fear memories, which renewed interest in the post-retrieval memory process of reconsolidation. Reconsolidation is a restabilization process triggered by the retrieval of the original memory (Duvarci and Nader 2004). Interventions that interfere with reconsolidation can persistently alter the expression of fear memories (Nader et al. 2000; Schiller et al. 2010). However, to derive a viable therapeutic technique based on disrupting reconsolidation, it is critical that both recently formed and older fear memories can be altered. Since memories of trauma are often formed long before treatment opportunities are available, it is important to characterize the effectiveness of reconsolidation for older memories. To date, there is little evidence in humans demonstrating the efficacy of targeting reconsolidation to diminish the expression of fear memories

>1 d old. The goal of the present study was to start to bridge this gap by targeting reconsolidation in 7-d-old fear memories.

Two primary techniques have been used to target the reconsolidation of fear memories: pharmacological and behavioral. These studies have examined fear memories using Pavlovian fear conditioning, in which an aversive unconditioned stimulus (UCS) is paired with a neutral conditioned stimulus (CS+). After a few pairings the CS+ acquires the ability to elicit a defensive or fear response, demonstrating the conditioned response (CR). Research in rodents has shown that Pavlovian fear acquisition, storage, and expression critically depend on the amygdala, with the lateral amygdala (LA) as the site of cued fear memory storage (LeDoux 2000).

Pharmacological studies have generally targeted the LA region when disrupting reconsolidation of cued fear memories. Since, like consolidation, reconsolidation requires protein synthesis (Nader et al. 2000; Alberini 2005), the direct infusion of a protein synthesis inhibitor (i.e., anisomycin) into the LA after CS+ reactivation eliminates the long-term expression of the CR in rats, presumably by disrupting the reconsolidation of the original fear memory (Nader et al. 2000). Several studies in rodents have shown that anisomycin can successfully disrupt the reconsolidation of older fear memories (14 d [Nader et al. 2000], 45 d [Debiec et al. 2002], 21 d [Frankland et al. 2006], 30 d [Einarsson and Nader 2012], 7 d [Hong et al. 2013]). These initial results are encouraging and suggest that disrupting reconsolidation may not depend on the age of the cued fear memory (but see Alberini 2011).

Since the use of anisomycin is toxic in humans, another line of research has focused on the noradrenergic system. In rats, blocking noradrenergic transmission with a  $\beta$ -adrenergic

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antagonist (i.e., propranolol) in the LA after reactivation of the CS+ also appears to interfere with reconsolidation (Debiec and LeDoux 2004), whereas enhancing noradrenalin can facilitate it (Debiec et al. 2011). In rodents, propranolol has also been shown to effectively disrupt the reconsolidation of older conditioned fear memories (60 d [Debiec and LeDoux 2004], 2 d [Muravieva and Alberini 2010]). In humans, the use of propranolol to disrupt the reconsolidation of fear memories has yielded inconsistent findings (for review, see Lonergan et al. 2012). The vast majority of studies in humans have administered the drug prior to memory reactivation (e.g., Kindt et al. 2009; Poundja et al. 2012), thus potentially targeting memory retrieval, not reconsolidation (Muravieva and Alberini 2010). The few studies that have targeted the reconsolidation process with propranolol have demonstrated limited effectiveness (Soeter and Kindt 2012), with disruption of potentiated startle as a measure of fear memory expression, but not autonomic (i.e., skin conductance or SCR) or expectancy measures. A study attempting to target the reconsolidation of older fear memories in patients with PTSD administered propranolol or placebo after patients recalled personal traumatic events (Brunet et al. 2008). Patients given propranolol showed decreased autonomic measures of fear (i.e., SCR and heart rate) a week later, relative to the placebo group; however, this study lacked a non-reactivation control to rule out a general dampening effect of propranolol on autonomic arousal.

Given the toxic effects of most drugs used to target reconsolidation in animal models and the limited results in humans using propranolol, perhaps the most feasible approach is a behavioral intervention that modifies the learned association. The behavioral interference of reconsolidation is based on the premise that the purpose of reconsolidation is to allow an opportunity for an older memory to be updated or strengthened with subsequent retrieval. Precisely timing standard extinction training after memory reactivation to coincide with the reconsolidation process has been shown to result in persistent fear reduction in rodents (Monfils et al. 2009) and humans (Schiller et al. 2010), in comparison to standard extinction. In addition, the behavioral interference of reconsolidation results in plasticity-related changes in the LA in rodents (Monfils et al. 2009; Clem and Haganir 2010) and diminished blood oxygenation level dependent responses in the amygdala (Agren et al. 2012) and the prefrontal cortex (Schiller et al. 2013) in humans, supporting the notion that this behavioral technique can alter the original fear memory.

Although the effectiveness of this technique has not been investigated in older conditioned fear memories in humans, this has been explored in rodents, and appetitive memories have been examined in humans. Clem and Haganir (2010) found that the behavioral interference of reconsolidation of conditioned fear memories resulted in persistent fear reduction and enhanced synaptic plasticity within the LA, but only in 1-d-old memories. If they waited a week before performing the reconsolidation manipulation, the reactivation–extinction group did not differ from the standard extinction group. These results are in contrast to findings by Xue and colleagues (2012) examining appetitive conditioned place preference in rodents, and drug craving in human addicts. They found that a similar reactivation–extinction/exposure procedure designed to alter the reconsolidation of appetitive memories led to a lasting reduction in expression of 2-d-old conditioned place preference memories in rodents, and a craving reduction in addicts whose drug-taking memories are presumably much older.

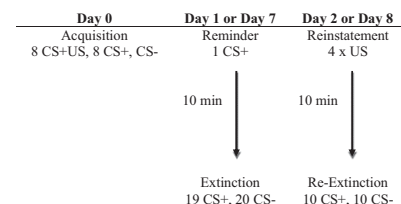
To assess if older conditioned fear memories can be altered by behaviorally targeting reconsolidation in humans, we adapted a paradigm from Schiller et al. (2010), which demonstrated the long-term effectiveness of this manipulation in 1-d-old memories. Eighty healthy participants were included in the final analysis ( $n = 79$  were excluded based on the studies' exclusion criteria)

(see Supplemental Material for exclusion criteria, demographic information, and questionnaires). Participants were randomly assigned to one of the four experimental groups: Reactivation Day 1, No Reactivation Day 1, Reactivation Day 7, and No Reactivation Day 7. The experiment consisted of three sessions (Fig. 1). During the first session (Day 0) all participants underwent fear conditioning using a discrimination paradigm: one colored square (CS+) was paired with an aversive electric shock (UCS) on half of the trials (eight CS+US and eight CS+ trials, 50% reinforcement), whereas a differently colored square (CS−) was never paired with a shock (ten CS−). Every trial consisted of a CS presentation (4 sec) followed by an inter-trial interval (10–12 sec) during which a fixation cross was presented. In CS+US trials a shock was administered 3.8 sec after CS onset and coterminated with the CS.

The second session was conducted either 1 or 7 d after fear acquisition. Half of the participants underwent extinction training after memory reactivation (Reactivation groups) and the other half underwent standard extinction without prior memory reactivation (No Reactivation groups). In order to reactivate the original fear memory both Reactivation groups received a reminder cue (a single CS+ trial) followed by a 10-min break during which a TV show episode (The Simpsons) was presented. Extinction training followed (i.e., the repeated presentation of CS+ and CS− without reinforcement). Both No Reactivation groups watched the same TV show episode prior to extinction, but immediately after the experimental setup without any reminder cue (see Schiller et al. 2010). This design resulted in four groups: The Reactivation Day 1 group returned to the laboratory 24 h after the first session and received a reminder cue prior to extinction training. The No Reactivation Day 1 group also returned after 24 h, but underwent extinction training only. The Reactivation Day 7 group returned after 7 d and received a reminder cue prior to extinction training whereas the No Reactivation Day 7 group returned after 7 d but did not receive a reminder cue. During extinction training all participants received 20 CS− trials. The number of CS+ trials was adjusted to account for the CS+ reminder trial (i.e., No Reactivation groups received 20 CS+ trials whereas Reactivation groups received only 19 CS+ trials).

The third session was conducted 1 d after the second session. The procedure was the same for all participants. To reinstate the fear memory, participants were exposed to four unsignaled shocks. After a 10-min break, during which all participants watched the same TV show episode (The Simpsons), a reextinction period followed (10 CS+ and 10 CS−).

The CR was defined as the mean differential SCR response (i.e., mean CS+ minus mean CS−). Mean CRs were calculated for early (first four trials) and late (last four trials) acquisition and extinction. In order to examine the return of fear after



**Figure 1.** Four different experimental groups: Reactivation Day 1, No Reactivation Day 1, Reactivation Day 7, and No Reactivation Day 7. All groups underwent acquisition on Day 0. Half the groups returned a day later to undergo extinction training either with (Reactivation Day 1 group) or without (No Reactivation Day 1 group) a reminder and on Day 2 for fear reinstatement and reextinction. The other two groups returned a week later to undergo extinction training either with (Reactivation Day 7 group) or without (No Reactivation Day 7 group) a reminder cue. These two groups underwent reinstatement and reextinction on Day 8.

reinstatement, we assessed the CR to the first trial of reextinction. Additionally, to assess the recovery of fear from extinction to reextinction we calculated a fear recovery index (i.e., late extinction CR minus first reextinction CR).

Fear acquisition was confirmed with a two-way analysis of variance (ANOVA), Group (Reactivation Day 1, No Reactivation Day 1, Reactivation Day 7, and No Reactivation Day 7)  $\times$  Time (early and late CR). Participants' CR increased significantly over time ( $F_{(3,79)} = 19.21$ ,  $P < 0.001$ ,  $\eta = 0.20$ ); there was no group effect or interaction. A follow-up  $t$ -test across all participants showed that the CR differed significantly from zero in both early ( $t_{(79)} = 8.3$ ,  $P < 0.001$ ) and late ( $t_{(79)} = 15.27$ ,  $P < 0.001$ ) acquisition. The same approach was used to confirm fear extinction. Participants' CR decreased significantly over time ( $F_{(3,79)} = 60.07$ ,  $P < 0.001$ ,  $\eta = 0.44$ ); there was no group effect or interaction. A follow-up  $t$ -test across all participants showed that participants' CR differed significantly from zero at the beginning of extinction ( $t_{(79)} = 8.5$ ,  $P < 0.001$ ), but was not significantly different from zero at the end of extinction ( $t_{(79)} = 1.76$ ,  $P = 0.08$ ). These results are not surprising given our exclusion criteria (see Supplemental Material) and demonstrate that participants successfully acquired and extinguished fear (Fig. 2).

To test for differences in reinstatement between groups, we conducted a one-way ANOVA for the first CR during reextinction. There was a main effect of group ( $F_{(3,79)} = 3.99$ ,  $P < 0.05$ ). Independent samples  $t$ -tests showed that participants who underwent standard extinction training exhibited significantly higher CRs than those who received a reminder cue prior to extinction (No Reactivation Day 1 group vs. Reactivation Day 1 group,  $t_{(38)} = 2.36$ ,  $P < 0.05$ ; No Reaction Day 7 group vs. Reactivation Day 7 group,  $t_{(38)} = 2.18$ ,  $P < 0.05$ ). There was no difference between both Reactivation groups ( $t_{(79)} = 0.97$ ,  $P = 0.34$ ) and between both No Reactivation groups ( $t_{(79)} = 0.87$ ,  $P = 0.39$ ). Follow-up  $t$ -tests showed that the CR in both Reactivation groups was not significantly different from zero (Reactivation Day 1 group,  $t_{(19)} = 1.19$ ,  $P = 0.25$ ; Reactivation Day 7 group,  $t_{(19)} = -0.25$ ,  $P = 0.81$ ). In contrast, in both No Reactivation groups the CR was significantly different from zero (No Reactivation Day 1 group,  $t_{(19)} = 4$ ,  $P < 0.01$ ; No Reactivation Day 7 group,  $t_{(19)} = 2.74$ ,  $P < 0.05$ ). Similar results were obtained when assessing the fear recovery index (see Supplemental Material).

The present findings suggest that, similar to young memories, older fear memories can also be updated using extinction training after memory reactivation. We showed that the extinction of 1-d-old and 7-d-old fear memories during the reconsolidation window successfully diminished the fear response after fear reinstatement. These results are consistent with rodent studies using pharmacological blockade of reconsolidation to successfully modify older fear memories (Nader et al. 2000; Debiec et al. 2002). They offer support for the notion that memories are suscep-

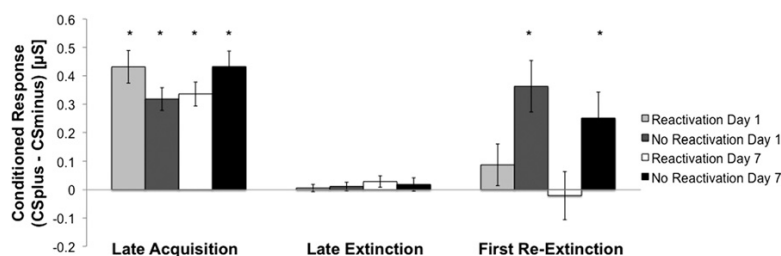
tible to modification even after initial consolidation is terminated when new, safe information is introduced during reconsolidation. This further underscores the adaptive value of reconsolidation.

Interestingly, the present results are incongruent with the findings of Clem and Haganir (2010), who showed that a comparable behavioral intervention in mice did not prevent the return of 7-d-old fear memories. This might suggest some differences in age-related memory processes between species, specifically that the susceptibility of memories to modifications lasts longer in humans vs. rodents. However, notable differences between these studies might also explain the opposing results. First, the strength of the fear memory might differ. We observed robust fear conditioning in our final sample, although we excluded around 50% of our initial study population because the conditioning or extinction effects were not robust (see Supplemental Material for exclusion criteria). Due to ethical constraints, laboratory-generated fear memories in humans are always mild. Second, although the molecular mechanisms of memory aging are similar across species, the time line might be different. A simple comparison based on the different life expectancies in humans ( $\sim 70$  yr) and mice ( $\sim 2$  yr) shows that 7 d in mice roughly equal 70 d in humans (see Quinn 2005).

Suzuki et al. (2004) addressed both of these concerns—strength and age of memory—in a contextual fear conditioning study in mice. The authors showed that reconsolidation of stronger contextual fear memories (i.e., three foot shocks instead of one) could not be blocked with anisomycin. However, if the reactivation was intensified (i.e., longer reexposure to the training context), anisomycin resulted in a diminished fear response. In a similar vein, older contextual fear memories (8 wk) were not susceptible to change by pharmacological manipulation unless prolonged reactivation sessions were conducted (Suzuki et al. 2004). These results suggest that older and stronger fear memories can also be updated under the right circumstances. Therefore, one could speculate that a behavioral intervention in mice after a prolonged memory reactivation period might also render older fear memories labile and lead to a persistently diminished fear response. However, it is necessary to examine this in future research.

It should be noted that the present study was intended to closely mirror the nonhuman animal research that inspired us (Clem and Haganir 2010), and therefore has two limitations. First, we excluded participants who showed no evidence of fear acquisition or extinction from further participation. In studies examining techniques to diminish fear (e.g., extinction and reconsolidation) across species this is a common exclusion criterion because fear acquisition and extinction are prerequisites to study fear recovery following manipulations of reconsolidation (e.g., Yang et al. 2006; Sotres-Bayon et al. 2009; Kindt and Soeter 2011). However, fear conditioning procedures typically used in humans are less robust in rodents for a few reasons. First, ethical

constraints require the intensity of the UCS to be relatively mild and not painful (see above), thus reducing its aversive nature. Second, the strength of the non-invasive, autonomic physiological response typically assessed in human fear conditioning (i.e., SCR) can vary with participants' race (Johnson and Landon 1965), age, sex, as well as the weather and room temperature (Venables and Mitchell 1996). We did not control for these factors in participant selection or data collection. Due to these constraints, we excluded a significantly higher proportion of participants who failed to meet the exclusion criteria than would



**Figure 2.** Participants in all groups showed an increased CR after fear acquisition (Day 0) and a diminished CR during extinction (Day 1 or Day 7). The CR during reextinction after fear reinstatement (Day 2 or Day 8) was increased only in the No Reactivation groups.

be typical in research with rodents, but the criteria were the same. Second, we did not acquire UCS expectancy ratings, a cognitive measure on which participants indicate the likelihood of the UCS on each trial and which is used in some human fear conditioning studies. Although the use of this measure may have resulted in a more robust assessment of fear conditioning and the loss of fewer participants, we chose not to use it because assessing explicit cognitive knowledge is obviously not possible in research in rodents and would have limited the generalizability between our paradigm and the findings in rodents. In addition, emphasizing explicit knowledge of the CS–UCS relationship has been shown to alter the nature of fear learning (Olsson and Phelps 2004; Atlas et al., pers. comm.) and the neural substrates mediating this learning (Funayama et al. 2001; Coppens et al. 2009). For these reasons, we limited our fear assessment to a noninvasive, autonomic measure.

The present study is an important step in further characterizing the boundaries within which reconsolidation update mechanisms are viable in humans. As research on reconsolidation progresses, it is becoming increasingly clear that several factors are linked to the effectiveness of targeting reconsolidation to prevent fear (Auber et al. 2013). Understanding the boundary conditions (e.g., strength and age of memory) is critical in order to translate these findings to useful clinical interventions. The present results are only an initial step toward understanding the potential temporal limitations of reconsolidation and further studies with fear memories older than 4 wk are necessary to match the temporal characteristics of PTSD and to distinguish if these results can potentially be translated to acute traumatic fear memories or also to older traumatic fear memories (DSM V, American Psychiatric Association 2013). The present results, however, suggest that the behavioral interference with the reconsolidation of fear memories could be a useful technique to modify fear memories regardless of their age.

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## **Supplementary Methods**

### Participants

The final sample included 80 participants (46 female; age mean 23.21, age range 18-57). In order to examine the recovery of conditioned fear, participants needed to both reliably acquire and extinguish conditioned fear prior to the recovery test (reinstatement). This led to the following exclusion criteria (see also, Schiller et al. 2010; Kindt and Soeter 2011). If we were unable to assess a reliable SCR response during acquisition (i.e. non-responders) participants were excluded and were not tested further ( $n = 6$ ). Participants were also excluded after acquisition if they failed to demonstrate robust conditioned responses as assessed with SCR (i.e., participants who's late CR was less than  $0.1\mu\text{S}$  were excluded;  $n = 40$ ). After the second, the extinction session participants were excluded from further participation if their SCR was not indicative of fear extinction (i.e., late CR  $> 0.1\mu\text{S}$ ;  $n = 30$ ). Only participants who met these criteria and attended the third session were included in the final analysis ( $n = 3$  failed to return). All participants gave informed consent and were paid for participation.

### Questionnaires

After the last session the following psychometric measures were acquired: Becks Depression Inventory-II (BDI-II; Beck et al. 1996), State Trait Anxiety Inventory (STATE and STAIT; Spielberger et al. 1983), and the Penn State Worry Questionnaire (PSWQ; Meyer et al. 1990). All acquired measures are in a normal range (BDI: mean ( $M$ ) = 6.46, standard deviation ( $SD$ ) = 7.64; STAIT:  $M = 36.01$ ,  $SD = 11.71$ ; STAIT:  $M = 41.01$ ,  $SD = 11.08$ ; PSWQ:  $M = 44$ ,  $SD = 8.69$ ) and do not vary significantly between groups (BDI-II,  $F_{(3,79)} = 5.02$ ,  $P = .68$ ; STAIT,  $F_{(3,79)} = .17$ ,  $P = .92$ ; STAIT,  $F_{(3,79)} = .25$ ,  $P = .86$ ; PSWQ,  $F_{(3,79)} = .36$ ,  $P = .78$ ). None of the subjective measures correlated with the SCR.

### Behavioral paradigm

The experiment consisted of three sessions: acquisition, reactivation and/or extinction, and reinstatement and re-extinction. The first two sessions were conducted either 24 h apart (Reactivation Day 1 and No Reactivation Day 1 group) or 7 d apart (Reactivation Day 7 and No Reactivation Day 7 group). The third session was always 24 h after the second. The CS+ was a yellow square and the CS- was a blue square. Trial order was pseudorandomized such that there were no more than two consecutive

trials of each type. Two different trial orders were created for each day and participants were randomly assigned to one order. The SCR and shock electrodes were attached during all sessions and the shock stimulator was turned on all the time, except during the breaks (see Schiller et al. 2010).

#### Psychophysiological stimulation

Mild electric shocks (US) were administered to the right wrist with a grass medical instruments stimulator (West Warwick, Rhode Island). To determine the individual shock level, participants received a very mild shock (20 V), which was gradually increased until participants reported the experience to be uncomfortable but not painful (maximal possible level 60 V). The shocks were given for 200 ms, with a current of 50 pulses per second. The shock level remained the same on all three days.

#### Psychophysiological assessment

To record SCR two Ag-AgCl electrodes were attached to the first and second fingers of the left hand between first and second phalanges (BIOPAC Systems, Santa Barbara, CA, USA). AcqKnowledge 3.92 software (BIOPAC Systems) was used to filter and smooth the raw SCR data offline. SCRs whose onset occurred within a 0.5 – 4.5 s latency window following CS onset were scored as a base-to-peak amplitude difference and further square root transformed and scaled relative to each participant's mean SCR to the US.

#### Statistical analyses

In order to assure that we excluded any unconditioned response to the shock itself in our analysis of the CR only non-reinforced CS+ trials were included. The unconditioned response (UCR) was only examined as a manipulation check. We averaged the SCR to the reinforced CS+ trials during conditioning (day 0; 8 CS+UCS) and during reinstatement (day 2 or day 8; 4 CS+UCS). One-Way-ANOVAs revealed that the UCR did not differ between groups during conditioning,  $F_{(3,79)} = .34$ ,  $P = .8$ , and during reinstatement,  $F_{(3,79)} = 1.27$ ,  $P = .29$ .

The first trial of the extinction and re-extinction/recovery test (CS+ for half the participants and CS- for the other half – randomly assigned) was not included in the final analysis due to a large orienting response typically observed in the first trial of a session.

## Supplementary Results

### Fear recovery index

A one-way ANOVA with the recovery index showed that the return of fear from extinction to re-extinction varied significantly, main effect of group ( $F_{(3,79)} = 3.98$ ,  $P < .05$ ). Independent samples  $t$ -tests showed fear recovery only in participants' who underwent standard extinction training (No Reactivation Day 1 group compared to Reactivation Day 1 group,  $t_{(38)} = 2.35$ ,  $P < .05$ ; No Reactivation Day 6 group compared to Reactivation Day 6 group,  $t_{(38)} = 2.13$ ,  $P < .05$ ). Again, there was no difference between both Reactivation groups ( $t_{(38)} = 1.07$ ,  $P = .29$ ) and between both No Reactivation groups ( $t_{(38)} = .945$ ,  $P = .35$ ; Suppl. Fig 1.).

Additionally, we attained participants' subjective feelings elicited by each image at the end of each session ("How do you feel when seeing this image?"; on a scale from 1 (positive) to 5 (negative)). A Multiple ANOVA showed a significant Main Effect of Time,  $F_{(2,79)} = 63.49$ ,  $P < .001$ , and a significant Time X CS Interaction,  $F_{(2,79)} = 137.93$ ,  $P < .001$ . Post-hoc  $t$ -tests revealed that this interaction was due to a less negative response to the CSplus and a less positive response to the CSminus after fear extinction (day 1/day 7) compared to fear acquisition (day 0). The CSplus rating decreased steady from day 0 to day 1/day 7,  $t_{(79)} = 8.71$ ,  $P < .001$ , and from day 1/day 7 to day 2/day 8,  $t_{(79)} = 3.07$ ,  $P < .05$ . In contrast, the CSminus rating was less positive on day 1/day 7 compared to day 0,  $t_{(79)} = 4.81$ ,  $P < .001$  and remained the same on day 1/day 7 and day 2/day 8,  $t_{(79)} = 1.18$ ,  $P = .24$ . Importantly, there was no Main Effect of Groups,  $F_{(3,79)} = 1.03$ ,  $P = .38$ .

## Supplementary References

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## Reconsolidation update can change old fear memory

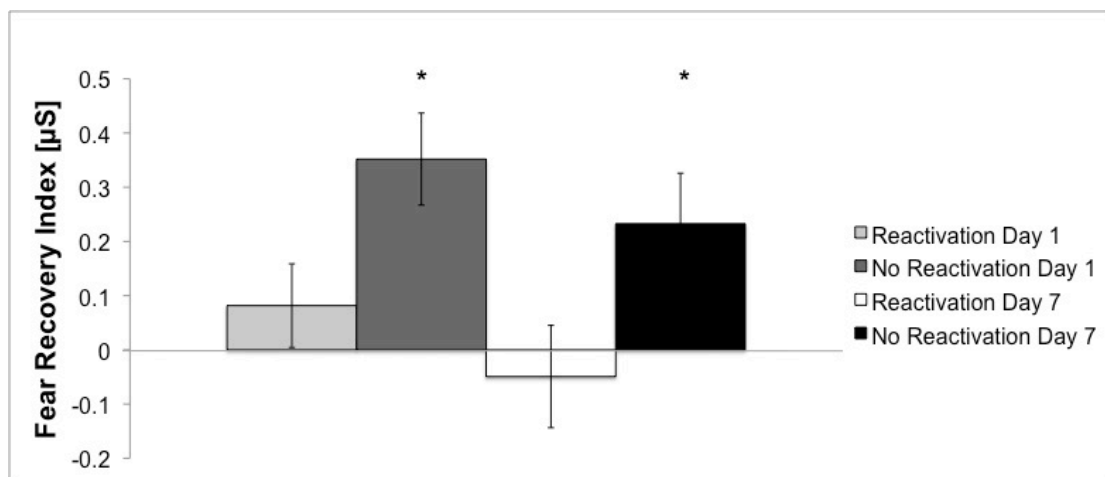
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### Supplementary Figure

#### *Supplementary Figure 1.*

Fear recovery index. The fear recovers from extinction to re-extinction only in the No Reactivation groups.



# Study 3

## **Physiological and neural correlates of worry and rumination: Support for the contrast avoidance model of worry**

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AH, JW, and ES designed the study. ES and MA did the laboratory assessment. ES preprocessed and analyzed the data with assistance of JW and MA. All authors contributed to the interpretation of the data and wrote the manuscript (first draft provided by ES).



## Physiological and neural correlates of worry and rumination: Support for the contrast avoidance model of worry

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### Abstract

The current experiments tested neural and physiological correlates of worry and rumination in comparison to thinking about neutral events. According to the avoidance model—stating that worry is a strategy to reduce intense emotions—physiological and neurobiological activity during worried thinking should not differ from activation during neutral thinking. According to the contrast avoidance model—stating that worry is a strategy to reduce abrupt shifts of emotions—activity should be increased. To test these competing models, we induced worry and neutral thinking in healthy participants using personal topics. A rumination condition was added to investigate the specificity of changes induced by the mental process. Two experiments were conducted assessing the effects on different response levels: (1) neural activation using fMRI, and (2) physiological response mobilization using startle and autonomic measures. During worry, participants showed a potentiated startle response and BOLD activity indicative of emotional network activation. These data partly support the contrast avoidance model of worry. Both mental processes showed elevated activity in a common network referred to as default network indicating self-referential activity.

**Descriptors:** Worry, Rumination, Neural networks, fMRI, Startle potentiation, Anxiety

Worry is a chain of repetitive thoughts that is experienced as relatively uncontrollable (Borkovec, Robinson, Pruzinsky, & DePree, 1983). Like anticipatory anxiety (Gray & McNaughton, 2000), it refers to an apprehensive expectation of negative events in the future. According to the avoidance model of worry proposed by Borkovec (1994), worry is considered a cognitive avoidance strategy. To reduce emotional arousal evoked by anticipated potential future threat, vivid emotional imagery is inhibited (Borkovec, 1994). This theory is supported by studies showing that neither worrying itself nor a subsequent presentation of emotional stimuli is associated with an enhanced physiological response (Borkovec & Hu, 1990; Llera & Newman, 2010). In line with Mowrer's (1947) two-stage theory of fear, this blunted emotional response is considered to function as a negative reinforcer for maintaining worry (Borkovec, 1994).

While the avoidance model of worry is a prominent model to explain the mechanisms of generalized anxiety disorder (GAD; Behar, DiMarco, Hekler, Mohlman, & Staples, 2009; Borkovec, 1994), it does not suffice to explain the heterogeneous findings regarding physiological activity during worry. It is particularly unclear to what extent Borkovec's findings were driven by

physiological responses during worry or if they only unfold during subsequent emotional periods. Supporting Borkovec's model, Peasely-Miklus and Vrana (2000) found stronger suppression of heart rate during fearful imagery after a period of worry than after a period of relaxation in victimization-fearful and victimization and speech-fearful female participants. This effect was driven by increased physiological activity (heart rate and corrugator activity) during the period where participants had to think about a sentence concerning their worries compared to thinking about a sentence of relaxation. This finding questions the hypothesis that worries might help to suppress emotional arousal. Similarly, Hofmann and colleagues (2005) observed an increase in heart rate during a period of worry about giving an impromptu speech compared to a baseline at the onset of the experiment and a period of relaxation.

As a consequence, Newman and Llera (2011) proposed the contrast avoidance model of worry. They suggested that worry is preferred exactly because it provokes a state of increased physiological arousal and negative affect. It is assumed that during this negative affective state the occurrence of potential threats can only increase the negative affect to a certain degree; sharp abrupt negative emotional contrasts can be avoided, and the individual remains under the impression of staying in charge (Newman & Llera, 2011). Llera and Newman (2010, 2014) found enhanced negative emotionality including an increase in sympathetic arousal during worry, which resulted in a reduced emotional reactivity to unpleasant film clips presented subsequently. While these models focus on a potential functional role of worry to explain why particularly patients with GAD tend to worry extensively about a number of

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events and activities, neurobiological approaches attempt to understand how neural networks are involved in the process of worrying itself.

Hoehn-Saric, Lee, McLeod, and Wong (2005) investigated regional cerebral blood flow (rCBF) using positron emission tomography (PET) while participants were instructed to think about either neutral statements heard previously or worries for 5 min. They observed less activity in the amygdala and insula during worry (Hoehn-Saric et al., 2005), which suggests reduced emotional activation during worried thinking. Further, no differences were found for skin conductance level and tonic heart rate between worry and neutral thinking in this study. In contrast, anticipation of unpleasant cues—a potential analogy to worry induction—resulted in an increased activation of the amygdala, the anterior insula, and the anterior cingulate (Carlson, Greenberg, Rubin, & Mujica-Parodi, 2011; Nitschke, Sarinopoulos, Mackiewicz, Schaefer, & Davidson, 2006; Onoda et al., 2008).

Given these inconsistent results in the literature, the first aim of the current study was to further investigate the neural networks involved in the process of worrying. In the study by Hoehn-Saric and colleagues (2005), worry was analyzed for 5 min. In the current study, we investigated the neural networks involved in the process of worrying and also assessed autonomic indices (skin conductance level and heart rate) for 15 s on a half-second basis. Moreover, we measured the blink component of the startle response—a cranial to caudal spreading wave of flexor movements elicited by any abrupt sensory stimulus. Animal and human studies have demonstrated that the startle response is reliably potentiated during fear conditioning or in an anxiety-provoking context (Davis & Whalen, 2001; Hamm, Richter, & Pané-Farré, 2014; Hamm & Weike, 2005). More importantly, for the current study, Cuthbert and colleagues (2003) demonstrated that startle potentiation is also observed during mentation (i.e., during memorizing and imagery of personally unpleasant scripts). The presentation of sentences describing ideographic fearful situations and the mental imagery of these scenes evokes an increase in autonomic arousal and a potentiation of the startle reflex across a broad spectrum of anxiety disorder patients (McTeague & Lang, 2012).

In the current study, two experiments were conducted to examine the effects of worry induction. In the first experiment, brain activity was measured during worried thinking using fMRI. In the second experiment, autonomic and startle responses were assessed using the same experimental procedure. To test whether worry induction leads to specific physiological changes and network activation in the brain, this study did not only use neutral sentences as reference stimuli but also other unpleasant thoughts, namely, ruminations.

Similar to worry, rumination does not lead to active problem solving but merely to a fixation on the problem (Nolen-Hoeksema, Wisco, & Lyobomirsky, 2008). However, in contrast to worry, rumination is elicited by negative thoughts about events in the past (Nolen-Hoeksema et al., 2008). To date, psychophysiological findings on the process of rumination are sparse. Rumination, instructed as concentration on one's feelings, has been found to be associated with increased skin conductance response (Sigmon, Dorhofer, Rohan, & Boulard, 2000) in high-anxiety sensitive females but not in nonanxious controls. Increased heart rate has been observed during rumination, induced by thinking abstractly about a distressing video (Ehring, Szeimies, & Schaffrick, 2009). Findings regarding anger rumination induced by the repeated recall of anger-provoking memories are controversial (no difference in heart rate: Glynn, Christenfeld, & Gerin, 2007, vs. an increase in heart rate: McClelland, Jones, & Douglas Gregg, 2009). Moreover,

ruminations of unpleasant past events were associated with an increased activation of frontal and temporal cortical areas (Cooney, Joorman, Eugene, Dennis, & Gotlib, 2010). Thus, the current study aims to investigate whether brain activation evoked during rumination can be discriminated from networks that are active during the process of worry.

In the study, personal topics were used to induce worry and rumination. Physiological and brain activity during worry and rumination were compared to activity elicited by thinking about personal but nonemotional neutral topics. If worry is a cognitive strategy to avoid emotional processing, there should not be a difference in physiological, neurobiological, and subjective activity between worry and neutral thinking. On the other hand, if worry is a strategy to create states of elevated physiological responding and negative affect, it should be associated with increased physiological arousal, negative affect, and neurobiological activity in the emotional networks compared to neutral thinking. On the neurobiological level, the focus of the analysis was on the amygdala due to its key role during encoding of emotional stimuli, including emotional words (Dolcos, LaBar, & Cabeza, 2004; Isenberg et al., 1999; Strange, Henson, Friston, & Dolan, 2000; Tabert et al., 2001), organizing emotional expressions (Phelps & LeDoux, 2005), and emotional memories (Dolcos, Denkova, & Dolcos, 2012; Dolcos, LaBar, & Cabeza, 2005). The insula was another region of interest because of its association with cognitively demanding emotional tasks and with self-induced or internally generated emotions (Phan, Wager, Taylor, & Liberzon, 2002). Beyond these regions, which are primarily involved in the generation of emotions, we expected an increased activity in the anterior cingulate gyrus (ACC), which is particularly engaged in emotional tasks with cognitive components (Phan, Wager, Taylor, & Liberzon, 2002). We also expected an increased activity in the dorsomedial prefrontal cortex (DMPFC) associated with self-referential processing (Fossati et al., 2003) and in the dorsolateral prefrontal cortex (DLPFC) associated with working memory processes and cognitive control (Smith & Jonides, 1999; Wager & Smith, 2003). Furthermore, we expected an increased activity in the hippocampus, particularly during rumination, since the task is associated with memory processes (Squire & Knowlton, 2000).

## Experiment 1: Neural Network Activation During Worry and Rumination

### Method

**Participants.** Twenty-four participants (12 women, all Caucasian,  $M_{\text{age}} = 23.25$  years, age range: 19–32 years) recruited from a student sample of the University of Greifswald took part in the study. All participants gave written informed consent to the experiment approved by the University of Greifswald ethics committee. Participants either received course credits (3 h) or a financial compensation (15 €) for participation. None of the participants reported clinical levels of psychopathology in self-report screening questionnaires.<sup>1</sup> Only those participants were included in the study who did not meet the exclusion criteria for the scanner session.<sup>2</sup>

1. Anxiety Sensitivity Index (ASI; Peterson & Reis, 1992),  $M = 17$ ,  $SD = 7.89$ ; Beck's Depression Inventory (BDI; Hautzinger, Bailer, & Keller, 1993),  $M = 6.5$ ,  $SD = 5.21$ ; State-Trait Anxiety Inventory (STAI; Laux, Glanzmann, Schaffner, & Spielberger, 1981),  $M = 36.33$ ,  $SD = 8.66$ ; Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990),  $M = 43.5$ ,  $SD = 12.9$ .

2. We screened for the usual MRI exclusion criteria: pregnancy, tattoos, metal pieces inside the body, claustrophobia, epilepsy, and glasses.

**Table 1.** *Examples of Personal Topics*

Personal topic	Worry	Rumination	Neutral
Description	"I am soon going to start a voice therapy because I have had problems with my voice for some time. I hope it works and I can sing again someday."	"Last year a good friend of mine died in an accident. I think about it a lot."	"I should give blood again. I haven't donated in a while."
Keyword	Voice	Name of the friend	Blood donation

**Stimulus materials.** Participants were asked to give a brief written description about three individual events or topics that they currently worry about, three topics they ruminate about, and three neutral events they currently think about (see Table 1 for an example). Worry and rumination were introduced as individual and abstract processes, primarily differentiated by their temporal orientation. Most studies comparing worry and rumination use such temporal distinction to discriminate both mental processes (e.g., Borkovec, Alcaine, & Behar, 2004; Hoyer, Gloster, & Herzberg, 2009; Nolen-Hoeksema et al., 2008). The instruction to generate worry descriptions was "Please describe three personal events or topics in the future that you currently worry about." The instruction to generate sentences to provoke rumination was "Please describe three personal events or topics from the past you currently ruminate about." Neutral descriptions were referred to as current events or topics that are emotionally neutral. In addition, participants were asked to provide a keyword for each topic. Across participants, most of the sentences in all conditions were related to family and relationships, work, finance, health, environmental issues, politics, travel plans, voluntary and leisure activities, shopping, as well as the weather. All responses were scanned for conceptual clarity, and it was ensured that there was no overlap in topics within each participant. In case of similarity between topics (e.g., rumination about unhealthy eating habits in the past and worrying about future health), participants were asked to provide distinct keywords and to focus subsequently on the different aspects of the topic.

**Procedure.** One day after the generation of the sentences, the extraction of the keywords, and the scanning of the fMRI exclusion criteria, participants took part in the fMRI experiment. Upon arrival at the University hospital, participants were instructed and placed in the fMRI scanner. The experiment consisted of 12 different trials, three trials of each condition (worry, rumination, neutral, and positive<sup>3</sup>). Three balanced orders were generated with no more than two successive trials of the same condition. Every trial was only presented once. At the beginning of each trial, the individual keyword and the corresponding instruction were presented for 30 s (e.g., "Now please worry about *individual keyword*") on a tilted mirror mounted on the head coil. As an additional manipulation check, participants rated their anxiety, depression, tension, and concentration on 5-point Likert scales ranging from 1 (*not at all*) to 5 (*extreme*). A 15-s free relaxation period followed during which the word *relaxation* was presented on the mirror. Then, a fixation cross was presented for 8 s to prepare the participant for the presentation of the next keyword. After the experimental task, anatomical scans were undertaken. Finally, participants were debriefed and received either class credit or financial compensation.

3. The positive condition did not differ from neutral contents and is therefore not reported in this manuscript for the sake of clarity.

**Apparatus.** MRI data were collected using a 3T Siemens Magnetom Verio scanner using a 12-channel head coil. At the beginning of each scanning session, field homogeneity was optimized by a shimming sequence, and a gradient echo field map was acquired for the unwarping procedure. During the experimental task, 518 volumes with 33 slices (2.5 mm thick, 1.25 mm gap) were acquired in transversal oblique direction (TR 2000 ms, TE 25 ms, flip angle 90°, FoV 192 mm, matrix 96 × 96, voxel size 2 mm × 2 mm × 2.5 mm). Afterward, a T1-weighted anatomical volume was recorded (MP-RAGE, 176 sagittal slices, TR 1690 ms, TE 2.52 ms, flip angle 90°, matrix 256 × 256, voxel size 1 mm × 1 mm × 1 mm).

**Data reduction and analysis.** Preprocessing and statistical analyses were realized using the statistical parametric mapping software (SPM8, Wellcome Trust Centre for Neuroimaging, London, UK). Unwarping of geometrically distorted EPIs was performed in the phase encoding direction using the FieldMap Toolbox. Preprocessing included spatial realignment, normalization into the MNI (Montreal Neurological Institute) space, and spatial smoothing (FWHM [full width half maximum] 6 mm). One participant was removed from the fMRI analysis due to movement (>1.5 mm), thus fMRI data could be analyzed from 23 participants. To correct for low-frequency components, a high-pass filter with a cutoff of 128 s was applied. Statistical analyses were performed using the general linear model as implemented in SPM8. On the first level, a design matrix was created for each participant based on a canonical hemodynamic response function with four regressors (worry, ruminate, positive, neutral). The six movement parameters estimated during the realignment procedure were introduced as covariates into the model. The following *t* contrasts were conducted for each model: worry > neutral, ruminate > neutral, worry > ruminate, and ruminate > worry. Based on previous findings, the following regions of interest (ROI) were constructed using the Wake Forest University PickAtlas (Tzourio-Mazoyer et al., 2002): ACC, amygdala, insula, hippocampus, DMPFC (medial superior frontal gyrus), DLPFC (inferior triangular and opercular frontal gyrus, middle and superior frontal gyrus), and the ITG (inferior temporal gyrus). Small volume correction was applied for directed ROI hypotheses with an uncorrected threshold of  $p \leq .001$  (see Schienle, Schäfer, Pignatelli, & Vaitl, 2009). Verbal report data were analyzed using SPSS 22.0 (SPSS for Windows, SPSS Inc.). Bonferroni correction was applied ( $p < .05/3 = p < .017$ ).

## Results

Participants reported significantly more anxiety, depression, and feelings of tension after worry and rumination than after thinking about neutral words, main effect of condition,  $F(2,23) = 33.46$ ,  $p < .001$ ,  $\eta_p^2 = .59$ ; 23.8,  $p < .001$ ,  $\eta_p^2 = .51$ ; 22.1,  $p < .001$ ,  $\eta_p^2 = .49$ , for anxiety, depression, and tension ratings, respectively (see Table 2, for means and standard errors). Furthermore, reports

**Table 2.** Means (Standard Errors) of the Tension, Anxiety, Depression, and Concentration Ratings in Experiment 1 ( $N = 24$ ) and Experiment 2 ( $N = 28$ )

Condition	Experiment 1	Experiment 2
Tension		
Worry	3.07 (.15)	3.18 (.17)
Ruminate	2.77 (.15)	3.27 (.22)
Neutral	2.03 (.17)	2.17 (.17)
Anxiety		
Worry	2.40 (.18)	2.81 (.2)
Ruminate	1.93 (.18)	2.31 (.2)
Neutral	1.26 (.08)	1.40 (.1)
Depression		
Worry	2.11 (.15)	2.66 (.23)
Ruminate	2.28 (.18)	2.89 (.21)
Neutral	1.44 (.08)	1.42 (.09)
Concentration		
Worry	3.76 (.11)	3.93 (.15)
Ruminate	3.54 (.11)	3.76 (.16)
Neutral	3.52 (.12)	3.56 (.15)

of anxiety and tension were significantly increased during worry compared to rumination,  $t(24) = 3.73, p < .05$ ;  $2.6, p < .05$ . There was no difference between worry and rumination for depression,  $t(24) = -1.77, p = .09$ . Participants reported no significant difference in concentration across all conditions,  $F(2,23) = 2.86, p = .07, \eta_p^2 = .11$ .

**BOLD response.** The BOLD response varied significantly between worry and neutral states (see Table 3 and Figure 1). Compared to

**Table 3.** Results of the ROI Analysis

Region	Side	MNI			Z score
		x	y	z	
Contrast: Worry minus neutral					
ACC	L	-8	22	26	3.00*
Insula	L	-36	-22	22	3.71**
DLPFC					
(Superior frontal gyrus)	L	-14	38	42	3.41*
(Opercular part of the inferior gyrus)	R	54	8	14	3.09*
Hippocampus	R	40	-32	-12	3.07*
ITG	L	-40	2	-36	3.6*
	R	40	-54	-8	4.41**
Contrast: Ruminate minus neutral					
Amygdala	L	-26	-4	-24	3.41**
ACC	R	10	32	12	4.63**
Insula	L	-26	26	8	3.94**
	R	38	-28	22	3.22*
DMPFC	L	-8	30	54	3.91*
DLPFC					
(Superior frontal gyrus)	L	-22	-8	56	4.36**
(Superior frontal gyrus)	R	16	24	38	4.37**
Hippocampus	L	-30	-20	-18	4.33**
	R	26	-38	8	3.7**
ITG	L	-46	6	-34	3.56*
	R	42	-66	-8	3.49*
Contrast: Ruminate minus worry					
Amygdala	L	-30	-2	-26	3.65**
ACC	R	16	44	20	3.17*
DMPFC	R	16	52	4	3.48**
DLPFC					
(Superior frontal gyrus)	R	18	24	38	3.88*
(Opercular part of the inferior gyrus)	L	-46	14	12	3.8*
Hippocampus	L	-30	-4	-26	3.03*

\* $p_{uncorr} \leq .001$ . \*\* $p_{FWE} < .05$ .

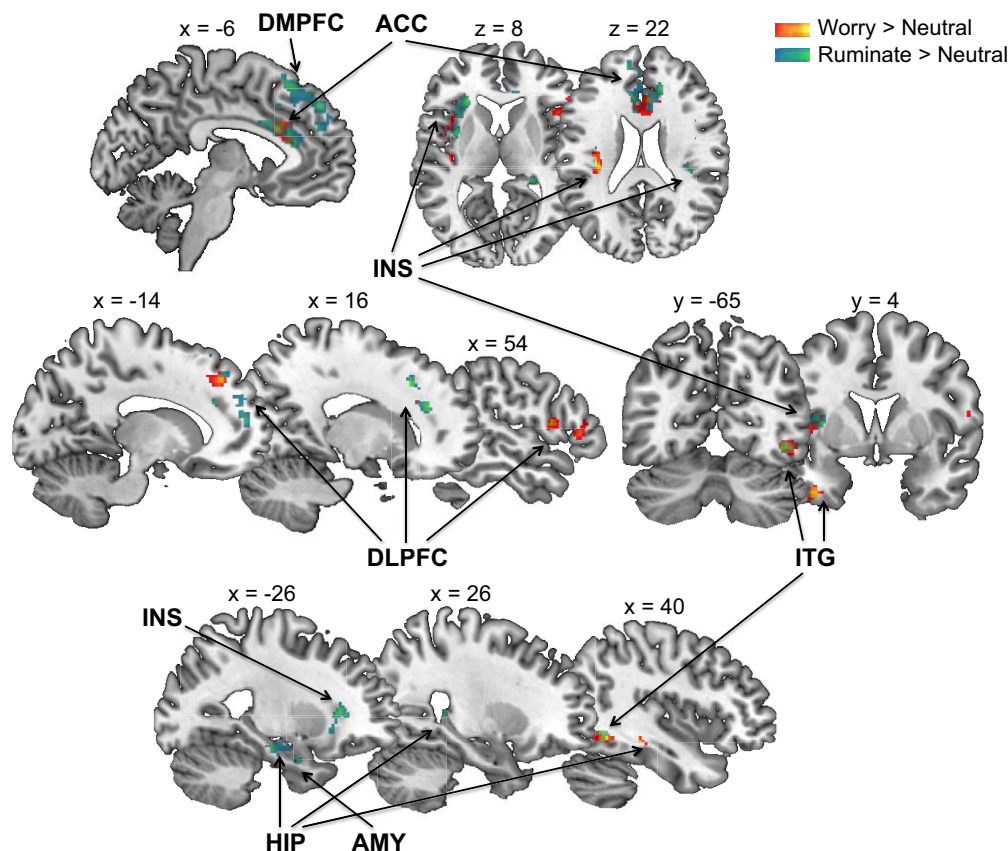
neutral, we observed significantly increased activity during worry in the ACC, the left insula, the bilateral DLPFC, the right hippocampus, and the bilateral ITG. Comparing rumination to thinking about neutral events, we found increased activation in the ACC, the left amygdala, the bilateral insula, the DMPFC, the bilateral DLPFC, the bilateral hippocampus, and the bilateral ITG. When we finally contrasted rumination with worry, we found increased activation during rumination in the ACC, the left amygdala, the DMPFC, the bilateral DLPFC, and the left hippocampus. There was no significantly increased activity in any brain area during worry compared to rumination.

## Discussion

Participants reported more unpleasant feelings during the induction of worry and rumination compared to neutral thinking, which suggests that the presented words indeed activated emotional networks. The fMRI data support this conclusion. In comparison with thinking about neutral events, an increased BOLD activity was found in the ACC, the left insula, the right hippocampus, the DLPFC, and the ITG when participants were instructed to think about future events they worry about or about personally negative events in the past. Compared with worrying about the future, rumination was associated with an increased activity in the ACC, the left hippocampus, the DMPFC, DLPFC, and the left amygdala.

These data are in line with previous findings about the ACC being crucially involved in worrisome thinking (Hoehn-Saric et al., 2005; Nitschke et al., 2009; Servaas, Riese, Ormel, & Aleman, 2014). However, even stronger activation of the ACC was found during rumination, suggesting that both mental processes are associated with increased activation of the ACC, probably because both rumination and worry activate self-referential schemata and are associated with heightened inward attention (Belzung, Willner, & Philippot, 2015; Servaas et al., 2014). This self-referential default mode network also involves the dorsal and medial prefrontal cortex. Accordingly, we observed an increased activity in the DLPFC in both repetitive thought processes as well as an increased activity in the DMPFC during rumination.

We observed no difference in activity in the amygdala during worry, but there was an increase in activity during rumination. This is in line with findings from instructed fear conditioning studies, which show that amygdala activity is unaffected by the anticipation of an aversive event (Mechias, Etkin, & Kalisch, 2010). Similarly previous studies about worry did not report an increase in activity in the amygdala (Hoehn-Saric et al., 2005; Servaas et al., 2014). In contrast, rumination about past aversive events was associated with a significantly increased amygdala activation. Instructing individuals to imagine personal negative scenes from the past also leads to an increased activation particularly in the amygdala, suggesting that the amygdala is involved in the recall of emotional memories (Costa, Lang, Sabatinelli, Versace, & Bradley, 2010; Denkova, Dolcos, & Dolcos, 2015). In accordance with this hypothesis, activity in the left hippocampus was increased during rumination compared to all other conditions. It has been suggested that particularly the left hippocampus is involved in context-dependent episodic or autobiographic memory (see Burgess, Maguire, & O'Keefe, 2002, for a review). More specifically, the left hippocampus is involved in the associative processing of sequential elements of an episode (Iglói, Doeller, Berthoz, Rondi-Reig, & Burgess, 2010). Such a repetitive replay of past episodes of failure or loss is the crucial characteristic of rumination. Increased activation of the left hippocampus was accompanied by increased activation of the left



**Figure 1.** Results of the ROI analysis. ROIs showing increased activity during worry compared to neutral are depicted in red-yellow: ACC, left insula, bilateral DLPFC, bilateral ITG, and right hippocampus. ROIs showing increased activity during ruminate compared to neutral are depicted in blue-green: DMPFC, ACC, bilateral insula, bilateral DLPFC, bilateral ITG, bilateral hippocampus, and left amygdala. For visualization purposes only, the results of all ROI analysis were extracted at  $p_{\text{uncorr}} = .05$  and overlaid on a standard template (ch2better.nii.gz) using MRICron ([www.cabiatl.com/mricro/mricro/mricro.html](http://www.cabiatl.com/mricro/mricro/mricro.html)). DMPFC = dorsomedial prefrontal cortex; ACC = anterior cingulate cortex; INS = insula; DLPFC = dorsolateral prefrontal cortex; ITG = inferior temporal cortex; HIP = hippocampus; AMY = amygdala.

amygdala during rumination, which suggests that emotional networks are closely connected to semantic information processing during repetitive thinking about aversive events from the past (Siegle & Thayer, 2004).

Additionally, we observed an increased activity in the ITG during worry and rumination. As part of the ventral visual processing stream, the ITG is involved in processing and imagining of emotional episodes (Sabatinelli, Bradley, Fitzsimmons, & Lang, 2005; Sabatinelli, Lang, Bradley, & Flaisch, 2006). This indicates that both worrying about the future and ruminating about the past rely on the generation of emotionally toned images. Similarly Borkovec and Inz (1990) observed that 26% of the worry period was characterized by imagery in nonanxious participants.

In the present study, we also observed an increase in activity in the insula in both repetitive thought processes. This finding stands in stark contrast to previous studies on worry (Hoehn-Saric et al., 2005; Servaas et al., 2014), which found reduced activity in the insula in worry compared to neutral conditions. However, considering that the insula is involved in the perception of feeling states (Craig, 2003; Critchley, Wiens, Rotschein, Öhman, & Raymond, 2004) and the recall and generation of emotions (Damasio et al.,

2000), the present results indicate that participants indeed actively generated “worry and rumination feelings.” The verbal report data support this hypothesis.

The next experiment tested whether indices of autonomic arousal and defensive reflex behavior would also support this hypothesis and could thus be related to the brain network activation observed in the first experiment.

## Experiment 2: Changes in Reflex Behavior and Autonomic Arousal During Worry and Rumination

### Method

**Participants, stimulus materials, and procedure.** Twenty-nine right-handed participants (17 women, all Caucasian,  $M_{\text{age}} = 22.72$ , age range: 19–34 years) who did not take part in the first experiment were recruited from a student sample of the University of Greifswald. All participants gave written informed consent to the experiment approved by the University of Greifswald ethics committee. Participants either received course credits (3 h) or a financial compensation (13 €) for participation. None of the participants

reported clinical levels of psychopathology in self-report screening questionnaires.<sup>4</sup> Stimulus materials were obtained in the same fashion as in Experiment 1.

One day after the generation of the sentences and the extraction of the keywords, participants took part in the actual experiment. Upon arrival in the laboratory, participants were seated in a reclining chair located in a sound-attenuated and dimly lit experimental chamber. After attaching the sensors, the experimenter left the room to check the signal quality. The experimental conditions and the procedure were identical to Experiment 1.

**Apparatus.** The electrocardiogram (ECG) was obtained using an Einthoven lead II setup with three standard, electrolyte-filled Ag/AgCl electrodes (Marquette Hellige, Freiburg, Germany). The raw signal was filtered (0.1–13 Hz band-pass) and amplified using a Coulbourn S75-01 bioamplifier. The digital sampling rate was set to 100 Hz and was maintained during the entire experiment. Additionally, an online Shimizu R-wave trigger was applied that was stored separately with a sampling rate of 1000 Hz. Skin conductance was recorded from the hypothenar eminence of the participant's palmar surface of the right hand using a Coulbourn S71-22 skin conductance coupler. Two Ag/AgCl standard electrodes (8 mm diameter; Marquette Hellige) filled with a 0.05 M sodium chloride electrolyte medium were placed 15 mm apart, and a constant voltage of 0.5 V circulated across them. The signal was processed with a resolution of 0.01  $\mu$ S. Digital sampling at 10 Hz was maintained during the entire experiment.

Electromyography (EMG) activity was recorded over the left orbicularis oculi muscle to measure the eyeblink component of the startle response. Two electrolyte-filled (Marquette, Hellige) Ag/AgCl miniature surface electrodes (Sensormedics, Yorba Linda, CA) were attached beneath the lower eyelid. The raw EMG signal was amplified using a Coulbourn S75-01 amplifier with a 30 Hz high-pass filter and a Kemo KEM-VBF8-03 400 Hz low-pass filter. Digital sampling at 1000 Hz using a 12-bit A/D converter started 100 ms before and lasted 400 ms after the onset of the acoustic startle stimulus. The acoustic startle stimuli (a 50-ms burst of broadband 95 dB[A] white noise with a rise/fall time < 1 ms) were generated by a noise generator (S81-02; Coulbourn Instruments, Allentown, PA) and presented binaurally over headphones (MDR-CD 170, Sony). Offline filtering of the EMG data was conducted with a digital 60 Hz high-pass filter to remove eye movement artifacts. Additionally, the EMG data were integrated (time constant of 10 ms) and rectified. Eight startle probes were presented after checking all sensors to ensure stable baseline startle magnitudes. During the experiment, three startle probes were administered during each of the thinking periods (at 2–4 s, 14–16 s, 26–28 s).

**Data reduction and analysis.** The heart rate was derived from the ECG signal using software provided by the VPM data analysis package (Cook, Atkinson, & Lang, 1987). The interbeat intervals were checked and corrected whenever misplaced R-wave triggers had occurred (due to increased T waves or movement artifacts). The heart rate was calculated and exported afterward. The digital skin conductance level values were converted to microsiemens ( $\mu$ S). Five subjects were removed from the skin conductance level analysis and two subjects were removed from the heart rate analysis due to technical problems during the recording. Both skin conductance level and heart rate values were baseline-corrected by

subtracting the mean baseline, averaged over 2 s prior to the beginning of each trial, from every value in that trial. The skin conductance level and heart rate data were further averaged over three 10-s intervals for early, middle, and late thinking periods. Reflex eyeblinks were scored using a computer program (Globisch, Hamm, Schneider, & Vaitl, 1993) that identified onset (in ms) and peak amplitude (in  $\mu$ V). All blinks occurring within a 20–100 ms time interval were scored as a valid startle response if they reached the peak amplitude within 150 ms after the startle probe onset. Trials with clear movement artifacts or excessive baseline activity were rejected and treated as missing trials (maximum 11% per subject), whereas trials with no detectable response in the defined time interval were scored as zero magnitudes (maximum 19% per subject). Two subjects were removed from further startle analysis due to technical problems during recording. In order to standardize blink magnitudes to correct for interindividual variability unrelated to the experimental conditions, raw startle magnitudes were transformed to *z* scores for each individual (subtraction of each startle response magnitude from the individual mean and divided by the standard deviation of all blink magnitudes of this individual) and converted to *T* scores. Data were further averaged per time point (early, middle, late) and condition (worry, ruminate, neutral). Two subjects displayed more than one missing or zero response at the same time point under the same condition. For these time points, no mean was calculated, and the data for this time point were excluded from the overall analysis without discarding the two subjects completely.

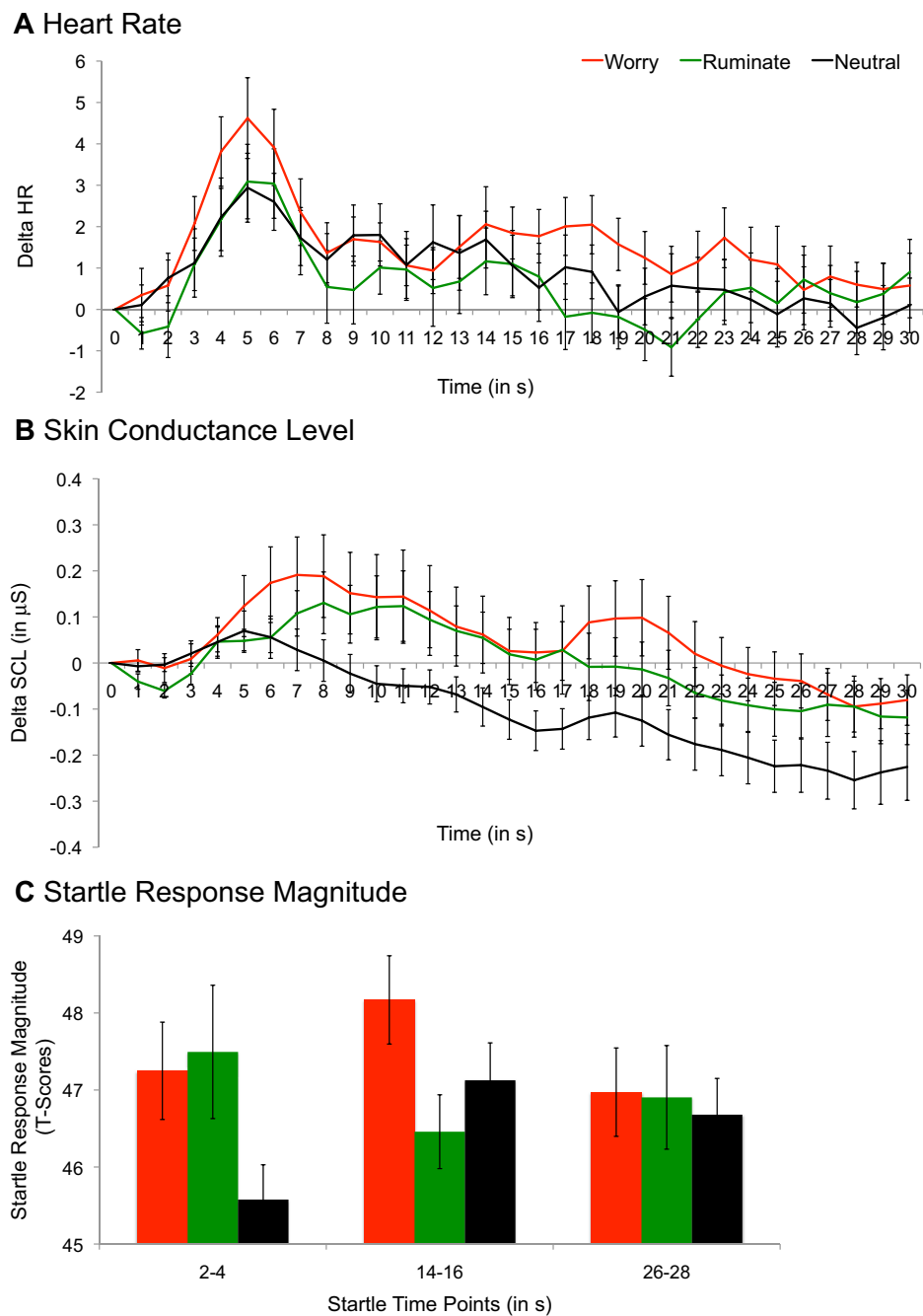
Physiological data were analyzed using a repeated measures analysis of variance (ANOVA) with within-variable condition (worry vs. ruminate vs. neutral) and time (three startle time points or 30 skin conductance level or 30 heart rate time points). Unless stated otherwise, all results reported met a significance level of  $\alpha < .05$ . The effect size was measured with the partial eta-squared ( $\eta_p^2$ ). Greenhouse-Geisser adjustments of degrees of freedom were used to control all effects involving repeated measures factors. Post hoc multiple comparisons were tested (worry > neutral, ruminate > neutral, worry > ruminate); Bonferroni correction was applied ( $p < .05/3 = p < .017$ ).

## Results

**Manipulation check.** Participants reported significantly more anxiety, depression, and feelings of tension during worry and rumination than during thinking about neutral words, main effect of condition,  $F(2,27) = 23.81$ ,  $p < .001$ ,  $\eta_p^2 = .47$ ; 29.99,  $p < .001$ ,  $\eta_p^2 = .54$ ; 16.06,  $p < .001$ ,  $\eta_p^2 = .37$ , for anxiety, depression, and tension ratings, respectively (see Table 2 for means and standard errors). Thus, verbal report data of Experiment 1 were replicated. Reports of anxiety were significantly increased during worry compared to rumination,  $t(28) = 2.70$ ,  $p < .05$ . There was no difference between worry and rumination for tension and depression ratings (tension:  $t(28) = -.49$ ,  $p = .63$ ; depression:  $t(28) = -1.15$ ,  $p = .26$ ). Participants were equally able to concentrate in all conditions,  $F(2,27) = 2.11$ ,  $p = .13$ ,  $\eta_p^2 = .07$ .

**Heart rate.** Figure 2A shows the changes in the heart rate after the onset of the instruction to worry, ruminate, or think about neutral events. After an initial acceleration, participants' heart rate significantly decreased during all conditions, main effect of time,  $F(2,26) = 10.53$ ,  $p < .001$ ,  $\eta_p^2 = 0.29$ . Although initial acceleration tended to be stronger during worry, we observed no significant differences between the conditions and no interaction Condition  $\times$  Time,  $F(2,26) = 1.23$ ,  $p = .30$ ;  $F(4,26) = .37$ ,  $p = .76$ .

4. ASI,  $M = 21.31$ ,  $SD = 11.00$ ; BDI,  $M = 7.45$ ,  $SD = 7.20$ ; STAI,  $M = 48.59$ ,  $SD = 13.56$ ; PSWQ,  $M = 48.9$ ,  $SD = 11.24$ .



**Figure 2.** Physiological change during worry, rumination, and neutral thinking. A: Baseline-corrected heart rate during worry, rumination, and neutral thinking averaged over 1-s intervals with standard error bars. B: Baseline-corrected skin conductance level during worry, rumination, and neutral thinking averaged over 1-s intervals with standard error bars. C: Startle response magnitude during worry, rumination, and neutral thinking at 2–4 s, 14–16 s, and 26–28 s.

**Skin conductance level.** Figure 2B depicts changes in the skin conductance level. The skin conductance level also varied significantly over time, main effect of time,  $F(2,23) = 36.68$ ,  $p < .001$ ,  $\eta_p^2 = .62$ . On a trend level, the skin conductance level was higher during worry and rumination than during neutral thinking, main

effect of condition,  $F(2,23) = 2.66$ ,  $p = .1$ ,  $\eta_p^2 = .10$ . We observed no interaction Condition  $\times$  Time,  $F(4,23) = 1.49$ ,  $p = .23$ .

**Startle response magnitudes.** Figure 2C shows the startle response magnitudes to probes presented at three different times

during the mental processes. Blink magnitudes were significantly modulated by the mental processes, main effect of condition,  $F(2,26) = 3.65$ ,  $p < .05$ ,  $\eta_p^2 = .13$ . This effect varied marginally across time, main effect of time,  $F(2,26) = 2.02$ ,  $p = .1$ ,  $\eta_p^2 = .08$ . We observed no interaction Condition  $\times$  Time,  $F(4,26) = .92$ ,  $p = .41$ . Blink magnitudes were significantly potentiated during worry at the first probe and marginally at the second probe,  $t(26) = 2.67$ ,  $p < .05$ ;  $1.72$ ,  $p = .1$ . Compared with neutral thinking, startle responses were also potentiated during the initial phase of rumination, but did not survive Bonferroni correction,  $t(26) = 2.17$ ,  $p = .04$ . At the second probe, worry blink magnitudes were significantly potentiated during worry compared to rumination,  $t(26) = 3.06$ ,  $p < .05$ . Startle responses at the third probe did not differ between the three conditions.

## Discussion

Worrying about future events was associated with a startle reflex potentiation indexing the activation of a subcortically mediated defensive motivational system (see Hamm & Weike, 2005). This startle potentiation was maintained throughout half of the worrying period and was no longer present at the end of the worry instruction. The worry period was further associated with a marginally elevated sweat gland activity. The other autonomic measure, heart rate activity, did not differ between conditions.

These findings partly support the contrast avoidance model of worry (Newman & Llera, 2011), which suggests that worrying about aversive future events is associated with heightened physiological activation indicative of a negative emotional state. However, the model also predicts that this heightened activation would be sustained during the entire worry period. In the present data, we observed an initial startle response potentiation (around 5 s), which was still present during half the worry period (recorded again at 15 s), but not at the end (around 27 s). Furthermore, autonomic arousal did not significantly differ between conditions. A number of alternative explanations may account for this pattern. First, participants may have found it too difficult to sustain repetitive worrying about a single event for the entire period of 30 s. A reminder cue or a specification of the worry content after 20 s may have produced sustained startle fear potentiation till the end of the worry period. Alternatively, shorter worry periods may be useful for a nonanxious sample. Future studies should also include a manipulation check to verify that participants thoroughly engage in the mental activity during the entire time.

Second, the worry instruction may not have been sufficiently explicit, and the concepts of worry and rumination may not have been clear enough. Participants may have needed a more thorough guidance in generating their worry topics and in activating their worries during the experiment. However, our design was driven by the motivation to least distort the personal quality of worries and to stay as close as possible to the natural worry process. In contrast to a specific phobia, worrying is highly personal and therefore difficult to induce with a standardized instruction. The activation of physiological arousal is stronger during the mental imagery of aversive episodes if descriptions of activated response units are incorporated into the narrative (see Lang, McTeague, & Bradley, 2014), which was neither the case in our nor in other studies investigating worry. Furthermore, the generation of the individual topics was guided by the temporal distinction between worry and rumination. Although we aimed at ensuring that there was no overlap in topics and keywords within participants, we could not exclude that both mental processes might show some overlap during the entire

period of mental activity (see Hoyer et al., 2009). Future studies should ensure conceptual clarity and rethink instructions to sufficiently activate personal worries.

Third, the power of the present study may be limited. On a trend level, the skin conductance level was elevated during worried thinking compared to neutral thinking. A repetition of the trials or a larger sample size may have yielded these differences significant. However, no trends were observed for heart rate activity. Fourth, the activation of defensive behavior might diminish as a result of adaptation during the rather long period of 30 s during which participants just viewed the keyword. And fifth, the nonanxious sample may not be used to maintaining the heightened level of worry as seen in GAD patients (e.g., Ray et al., 2009). Furthermore, it is possible that worry is not only quantitatively different in healthy controls compared to individuals suffering from GAD, but also has a fundamentally different quality. However, there has been some evidence for a continuum between normal and pathological worry and rumination (Goring & Papageorgiou, 2008) and research in support of the contrast avoidance model undertaken with GAD patients (e.g., Llera & Newman, 2014). With the available data, we cannot directly test which of these alternative explanations accounts for the nonsignificant autonomic response measures as well as the normalized startle response at the end of the worry period.

While the protective startle reflex is potentiated during the initial phase of worry and rumination, the process of rumination—also associated with increased ratings of anxiety, tension, and depression—is less associated with extended startle potentiation. Thus, extended activation of the physiological fear indicator seems to be specific for worry and not for negative effect in general.

## General Discussion

In the current study, we compared neural network activation, defensive response modulation, and physiological adaptations during worry, rumination, and thinking about neutral events. We found that both worrisome and ruminating thoughts induced an aversive emotional state as indicated by reports of elevated tension, anxiety, and depression. Furthermore, we found physiological changes associated with both mental processes. Moreover, both activated a common neural network that includes cingulate, frontal, and temporal cortical areas. These regions have been commonly referred to as the default network (Raichle et al., 2001), a term that reflects uninterrupted self-referential mental activity (Buckner, Andrews-Hanna, & Schacter, 2008; Buckner & Carroll, 2007). This network is also activated when individuals remember the past and imagine the future (see Schacter et al., 2012, for a review). It has been demonstrated that this default network is also activated during worry (Servaas et al., 2014). An increase in power may have revealed significant BOLD activity in further structures of the default mode network.

Emotional brain areas, including the ACC, the insula, and the DLPFC, which have often been found to be activated during processing of emotionally relevant information and during organizing emotional expression (Buhle et al., 2014; Davidson, Putnam, & Larson, 2000) were activated during worry and rumination—which also supports previous findings (Servaas et al., 2014). Particularly, the insula activation indicates the internal generation or the recall of emotions (Craig, 2003; Critchley et al., 2004; Phan et al., 2002). While there was a common neural network activation during both mental processes, there was no brain activation specific to worry

compared to rumination; however, rumination was characterized by an increased BOLD response in the amygdala, the ACC, the DMPFC, the DLPFC, and the hippocampus.

### The Process of Worrying

Thinking about an aversive personal event in the future resulted in higher ratings of anxiety and tension as well as a significant potentiation of the startle reflex. Since the startle reflex represents a very low-level measure of fear and anxiety, this finding supports the hypothesis that thinking about a worrisome topic indeed induced an emotional state of anxiety in these individuals. The fact that emotional and self-referential neural networks were activated (particularly the insula) further supports this hypothesis. However, the startle potentiation was not sustained during the entire worry period, the skin conductance level was only marginally elevated during worry compared to neutral, and no difference in the heart rate was observed.

The current data do not support the avoidance model of worry suggesting that worrying prevents emotional processing, because it is a thought-based process that is associated with inhibited somatic experience (Borkovec, 1994). Although thinking and verbal articulation of fear material produce fewer physiological responses than images of the same content (Vrana, Cuthbert, & Lang, 1989), our results suggest that the presentation of a personal keyword with the instruction “to worry” automatically activates a propositional network that not only contains stimulus and meaning representations but also representations of response output units that are activated once the network is activated (see Lang, 1979).

Rather, our findings support the contrast avoidance model (Newman & Llera, 2011) according to which worry is applied to prolong and maintain negative emotional states in order to prevent sharp negative contrasts. Our behavioral and neurobiological results show such a maintained negative emotional state. In contrast to the model, the heightened physiological activation is not sustained during the entire worry period. Furthermore, the current results cannot say whether physiological and neurobiological activation is stronger for individuals with high anxiety sensitivity or patients with GAD, as suggested in this model (Newman & Llera, 2011), because only healthy individuals were studied. However, the current experimental approach might be fruitful to test this assumption in future studies.

### The Process of Rumination

Rumination about negative events from the past resulted in an emotional state that was characterized by stronger feelings of depression and less anxiety and tension than under the condition of worry. In addition, an initial potentiation of the startle reflex was observed. Finally, we found an increased activation in the left amygdala and the left hippocampus during rumination. Although in the present study participants used personal topics both during worrying and rumination, these findings suggest that, compared to worry, rumination relies more strongly on autobiographical memory (Burgess et al., 2002; Cooney et al., 2010). This might be due to the fact that the content of current, future-related worries might be generated from experiences in the past and therefore might be similar to the content of rumination. Rumination itself is a process of indulging in the past and focusing on the negative affect (Nolen-Hoeksema et al., 2008). Interestingly, our data show that rumination about past events seems to be related to feelings of depression and less to emotional expression. Accordingly, rumination about negative events from the past is one of the central characteristics of depression (Beck 1967; Nolen-Hoeksema, 1991). Our results are in line with recent data from McTeague and colleagues (2009, 2010, 2012) that show a reduced startle reflex potentiation during imagery of personal threat scenes in anxiety patients who had a comorbid diagnosis of depression.

### Conclusions

The present research shows that thinking about negative events in the future and from the past activated the default network in the brain including the cingulate cortex as well as medial temporal and frontal cortical areas. Moreover, brain areas that are involved in emotion generation were also activated, which suggests that rumination and worry instructions evoke emotional states. This is supported by corresponding changes in the startle response and by data ascertained by verbal reports. However, this pattern was not or only marginally observed in autonomic nervous system measures and was not sustained during the entire worry period for the startle response. Therefore, these findings only partly support the contrast avoidance model of worry. That is, worrisome thoughts evoke an emotional response probably serving the function of avoiding an unexpected emotional shift (Newman & Llera, 2011). In contrast to worry, rumination is associated with a less stable startle potentiation as well as more pronounced amygdala and hippocampal activity indicating a stronger association with autobiographical and emotional memory processes.

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# Appendix B: List of publications

## In preparation

Steinfurth, E. C. K., Wendt, J., Geisler, F., Hamm, A. O., Thayer, J. F., & Koenig, J. (in prep.). Resting state high-frequency heart rate variability is associated with neural activity during explicit emotion regulation.

## 2017

Steinfurth, E. C. K., Alius, M. G., Wendt, J., & Hamm, A. O. (2017). Physiological and neural correlates of worry and rumination: Support for the contrast avoidance model of worry. *Psychophysiology*, 54(2), 161–171.

## 2014

Steinfurth, E. C. K., Kanen, J. W., Raio, C., Clem, R., Huganir, R. L., & Phelps, E. A. (2014). Young and old pavlovian fear memories can be modified with extinction training during reconsolidation in humans. *Learning and Memory*, 21, 338–341.

Steinfurth, E. C. K. & Hamm, A. O. (2014). Neurobiologische Grundlagen der Emotionsregulation. In M. A. Wirtz (Ed.) *Dorsch — Lexikon der Psychologie*, (18th ed., pp. 472). Bern: Hogrefe.

## 2013

Steinfurth, E. C. K., Wendt, J., & Hamm, A. O. (2013). Neurobiologische Grundlagen der Emotionsregulation. *Psychologische Rundschau*, 64(4), 208–216.



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