Extending the Concept of Emotion Regulation with Model-Based fMRI

Graduate School of
Systemic Neurosciences

LMU Munich

Dissertation

der Graduate School of Systemic Neurosciences

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Submitted by

Satja Mulej Bratec

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ABSTRACT

Effective emotion regulation is essential for our social and emotional well-being. Yet, the concept of emotion regulation, as it is conventionally regarded in the field, does not take important aspects of emotions and emotion regulation into account. The overarching aim of the current thesis was to include such missing aspects and thereby expand the concept of emotion regulation. The expansion occurred in two directions: firstly, the definition of emotion within the field of emotion regulation was widened to include the motivational aspect of emotions in terms of value-based prediction errors and their neural implementation; and secondly, an underestimated type of emotion regulation – the social emotion regulation – and its neural underpinnings were investigated.

Projects 1 and 2 of the current thesis expand the *emotion* part of emotion regulation. Project 1 investigated whether emotion regulation affects not only emotional response-related brain activity but also influences aversive prediction error-related activity, i.e., the motivation-related brain signal. We found that self-initiated reappraisal, a type of cognitive emotion regulation, indeed affected prediction error-related activity, such that this activity was enhanced in the ventral tegmental area, ventral striatum, insula and hippocampus, possibly via a prefrontal-tegmental pathway. Project 2 further examined the way emotion regulation affects emotions and prediction errors, by testing whether self-initiated reappraisal directly targets the brain network for motivated behaviour previously outlined by animal studies. We found that superior (in contrast to inferior) regulators affected the balance of competing influences of ventral striatal afferents on striatal aversive prediction error signals; they reduced the impact of subcortical striatal afferents (i.e., hippocampus, amygdala and ventral tegmental area), while keeping the influence of the prefrontal cortex on ventral striatal prediction errors constant. Inferior regulators, on the other hand, failed to supress subcortical inputs into the ventral striatum and instead counterproductively reduced the prefrontal influence on ventral striatal prediction error signals.

Projects 3 and 4 of the thesis extend the *regulation* part of emotion regulation. Project 3 explored the neural correlates of social cognitive emotion regulation, specifically reappraisal, and directly compared them with those of self-initiated reappraisal. We found that regions of the anterior, the medial parietal, and the lateral temporo-parietal default mode network were specifically involved in social emotion regulation, and that social regulation success and the default mode network involvement during regulation were related to participants' attachment security scores. Project 4 investigated social emotion modulation and its impact on two distinct types of emotional brain activity – emotional response- and aversive prediction error-related activity. We found – for the simple contrast of being with somebody versus being alone – a three-fold dissociation between signal types and insula subregions, including left and right anterior and posterior insula parts. Social emotion modulation reduced aversive stimulus-related activity in the posterior insula, while simultaneously increasing aversive prediction error-related activity in the anterior insula. Furthermore, the social effect on prediction error-related activity was positively associated with aversive learning in the right, but negatively in the left anterior insula.

Altogether, by expanding the concept of emotion regulation, projects of the current thesis provide new insights into both the effects and the neural underpinnings of three distinct emotion regulation types. Considering that problems in both intrapersonal emotion regulation and social interaction are linked to affective disorders, our findings might contribute to a better understanding of these disorders and the disorder-specific emotional and social impairments.

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General Introduction: Emotion Regulation in an Extended Context

Our emotions are subject to change at any moment. We can feel content and happy, but become highly distressed if we unexpectedly receive news that a loved one has been in a car accident. While emotions are an essential part of life, it is of paramount importance to our mental health that we are able to control or regulate our emotional responses (Eftekhari, Zoellner, & Vigil, 2009; Gross & Jazaieri, 2014; Gross & Muñoz, 1995; Ochsner, Silvers, & Buhle, 2012; Sheppes, Suri, & Gross, 2015). But emotions are much more than simple responses to our environment. By giving objects and events value, emotions motivate our actions, so that we strive to approach positive and avoid negative experiences (Lang & Bradley, 2010; Lang & Davis, 2006); emotion regulation might therefore additionally involve regulating parameters associated with motivated behaviour. On the other hand, our emotions are not only regulated by us, but can also be influenced by others; social emotion regulation is therefore an important, but often neglected, type of emotion regulation. In brief, projects of the current thesis aimed to incorporate 1) the motivational aspect of emotions into the concept of emotion regulation, thereby extending the notion of emotion regulation to additionally include the regulation of emotional-motivational responses; and 2) social emotion regulation as an important but largely underestimated type of emotion regulation. General Introduction is divided into four parts. The first part introduces emotion regulation as it is typically viewed, especially focusing on reappraisal, its neural underpinnings and individual differences in reappraisal ability. The second part focuses on the motivational aspect of emotions, introduces prediction errors, their neural correlates, and the neural network of motivated behaviour. The third part introduces social emotion modulation and regulation and the current knowledge on their neural basis. Finally, the fourth part outlines the aims of this thesis.

1.1 Emotion Regulation

Seen conventionally, emotion regulation denotes the process of controlling your emotional responses (for reviews, see Gross, 2015; Ochsner et al., 2012; Phillips, Ladouceur, & Drevets, 2008). In order to present the conventional view of emotion regulation, the current section portrays: a) different types of emotion regulation; b) reappraisal as a highly effective emotion regulation strategy; c) neural systems involved in the generation and regulation of emotion; and d) individual differences in reappraisal ability.

1.1.1 Emotion Generation and Types of Emotion Regulation

Conventional theories of emotion regulation clearly separate the concepts of emotion generation and emotion regulation. Because various types of emotion regulation occur at different stages of emotion generation, it is worthwhile to first briefly outline the process of emotion generation (Gross, 2015; Ochsner et al., 2012). The generation of emotion starts with the perception of a stimulus in a specific context (Barrett, Mesquita, Ochsner, & Gross, 2006; Ochsner et al., 2012). The stimulus can be internal (e.g. feeling of loneliness or contentment) or external (e.g. a snake or a smiling face). The context is important, since it can change the value of the stimulus and the associated emotion(s). For instance, noticing a snake in your son's playroom (therefore probably a snake toy) or on a forest footpath (therefore probably a dangerous animal) can drastically change the process of emotion generation. The second step of emotion generation involves the deployment of attention to certain stimuli or parts of stimuli, determining which stimuli will be focused on and therefore processed further (Ochsner et al., 2012). In the following step, the relevant stimulus or stimuli are appraised based on one's current needs, wishes, and goals, to determine their significance (i.e., are they positive or negative and to what extent). The fourth and final step of emotion generation embodies the emotional response, in terms of experience, behaviour and autonomic bodily changes (Ochsner et al., 2012).

Different types of emotion regulation can be categorised along a voluntary versus automatic dimension, as well as depending on which step of emotion generation

they are targeting, such as attentional control, cognitive change, or response modulation (Gross, 2015; Ochsner et al., 2012; Ochsner & Gross, 2005; Phillips et al., 2008). Automatic attentional control could be the modulation of spatial attention by emotional stimuli in a fear-conditioning paradigm (Armony, 2002), automatic cognitive change might involve covert learning that leads to an automatic adjustment of behaviour (e.g. in choosing risky or safe decisions in an Iowa gambling task) (Fukui, Murai, Fukuyama, Hayashi, & Hanakawa, 2005; Lawrence, Jollant, O'Daly, Zelaya, & Phillips, 2009), while automatic behavioural control may be represented by fear extinction (Gottfried & Dolan, 2004; Phelps, Delgado, Nearing, & LeDoux, 2004). On the other hand, voluntary attentional control might involve selective attention in a go/no go task (Goldstein et al., 2007), voluntary cognitive change usually represents a reappraisal or cognitive re-evaluation of an emotional event (Goldin, McRae, Ramel, & Gross, 2008; Kanske, Heissler, Schönfelder, Bongers, & Wessa, 2011; McRae et al., 2010; McRae, Ochsner, Mauss, Gabrieli, & Gross, 2008; Ochsner, Bunge, Gross, & Gabrieli, 2002; Ochsner et al., 2004; Phan et al., 2005; Walter et al., 2009), while behavioural control might involve suppressing one's emotional expression while watching negatively charged film clips (Goldin et al., 2008; Lévesque et al., 2003).

1.1.2 Reappraisal

Most research up to date has focused on deliberate cognitive emotion regulation, specifically reappraisal (for reviews and meta-analyses, see Buhle et al., 2014; Kalisch, 2009; Ochsner et al., 2012). Reappraisal is a complex cognitive emotion regulation strategy; it makes use of higher cognitive processes, such as language, memory and attention, in order to change one's appraisal of the stimulus, including the connection of the stimulus to oneself, with the goal of changing one's emotional response to that stimulus (Buhle et al., 2014; Gross, 2002; Kalisch, 2009). As an example, imagine that you are unexpectedly evicted from your apartment, which makes you anxious and angry. One way to make yourself feel better is by re-interpreting the situation. For instance, you could remind yourself how small and expensive the apartment really was, and how the loud neighbour above you was reducing your valuable hours of sleep – perhaps the eviction is an opportunity to find a better place to live.

One of the reasons why reappraisal is at the forefront of emotion regulation strategies is the fact that it is an incredibly effective strategy of modulating both subjective emotional feelings and physiological emotional reactions (Dillon & Labar, 2005; Gross, 2002; Gross & John, 2003; Kalisch et al., 2005; Webb, Miles, & Sheeran, 2012). The effects of reappraisal are also longer lasting than those of attentional control strategies (Kross & Ayduk, 2008; Ochsner et al., 2012; Ochsner & Gross, 2005). Furthermore, people that normally use reappraisal more often than suppression (i.e., a behavioural control regulation strategy) show advantages in mental health and social functioning (Eftekhari et al., 2009; Gross, 2002; Gross & John, 2003). Finally, reappraisal is an essential part of various forms of psychotherapy, such as cognitive behavioural therapy (Beck, 2005), further increasing the importance of this emotion regulation strategy.

1.1.3 The Neural Underpinnings of Emotion Regulation and Reappraisal

An extensive body of work has explored the neural systems underlying emotion regulation, especially reappraisal (for reviews, see Kalisch, 2009; Ochsner et al., 2012; Phillips et al., 2008). Since emotion regulation, in the conventional view, is seen as the process of controlling emotional responses, it is necessary to first consider the neural correlates of emotional responses, or more broadly, the correlates of emotion generation. The generation and experience of emotion is subserved by a range of brain regions, including amygdala, ventral striatum, insula, periaqueductal gray and ventromedial prefrontal cortex (PFC) (Kober et al., 2008; Ochsner et al., 2012; Phillips, Drevets, Rauch, & Lane, 2003). Employing a network approach, a meta-analysis of neuroimaging studies on emotion showed that regions involved in emotional processing could be grouped into six functional units: the core limbic group (areas traditionally viewed as 'emotion regions', including amygdala, ventral striatum, thalamus, hypothalamus, and periaqueductal gray), the lateral paralimbic group (including further parts of the ventral striatum and insula), the medial PFC group, the cognitive/motor group, the medial posterior group (including V1 and posterior cingulate), and the lateral occipital group, demonstrating both the high extent of the brain involved and the complexity of emotion generation (Kober et al., 2008). It is worth noting that there is an emerging view that there are in fact no areas or networks in the brain that are specialized for

different emotion categories or even emotion in general. Instead, domain-general large-scale brain networks, involved in basic emotional and non-emotional operations, are thought to interact to enable emotion perception and experience (Barrett & Satpute, 2013; K. A. Lindquist & Barrett, 2012; K. A. Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012).

The regulation of emotion is likewise subserved by an extensive network, mainly comprising frontal and parietal regions (Ochsner et al., 2012; Phillips et al., 2008). A distinction between automatic and voluntary emotion regulation has been proposed in the PFC: a lateral PFC system, including dorsolateral PFC and ventrolateral PFC, may be involved in voluntary emotion regulation processes, while a medial PFC system, including medial orbitofrontal cortex, anterior cingulate and the dorsomedial PFC, might be involved in automatic emotion regulation processes (Phillips et al., 2008). Reappraisal, the regulation type of choice for the first and second projects of this thesis, has been investigated most extensively. Regions involved in the process of reappraisal include the dorsolateral PFC, ventrolateral PFC, dorsomedial PFC and inferior parietal areas (Buhle et al., 2014; Kalisch, 2009; Kohn et al., 2013; Ochsner et al., 2012; Phillips et al., 2008). The dorsolateral PFC and the inferior parietal cortex are typically associated with working memory and selective attention, and therefore provide the means to hold reappraisal strategies in mind and to attend to relevant features of the stimuli (Wager & Smith, 2003; Wager, Jonides, & Reading, 2004). Ventrolateral PFC is involved in selecting goal-relevant information from memory, and can therefore help select the appropriate reappraisal strategy (Badre & Wagner, 2007). Finally, dorsomedial PFC, associated with accrediting mental states, might help with keeping track of one's emotional state (Olsson & Ochsner, 2008). In contrast, regions whose activity is typically suppressed during reappraisal, in principle span the emotion generation network described in the previous paragraph, but most commonly include amygdala, ventral striatum and insula (for a review, see Ochsner et al., 2012).

When investigating the neural underpinnings of emotion regulation, it is crucial to consider not only activation and de-activation brain patterns, but to also examine functional connections between the relevant brain regions and how these

connectivity patterns might be changed during emotion regulation. A growing number of studies have focused on connectivity rather then activity changes during emotion regulation, again typically utilizing reappraisal as the regulation of choice. For instance, a recent study, using dynamic causal modelling, focused on the connectivity among PFC regions involved in emotion regulation, and demonstrated an increase of excitatory changes from dorsolateral PFC to ventrolateral PFC, and an increase of inhibitory changes from ventrolateral PFC to dorsolateral PFC, possibly representing the choice of a reappraisal strategy (Morawetz, Bode, Baudewig, Kirilina, & Heekeren, 2015). Since amygdala is the most common region whose activity is suppressed during reappraisal (Buhle et al., 2014), some studies have examined whether the connectivity between amygdala and regulatory regions might be increased during regulation (Banks, Eddy, Angstadt, Nathan, & Phan, 2007; Erk et al., 2010). Indeed, amygdala increased its connectivity with dorsolateral PFC, dorsomedial PFC, orbitofrontal cortex and anterior cingulate in one study (Banks et al., 2007), and with dorsolateral PFC, ventromedial PFC, inferior parietal cortex and posterior cingulate in another study (Erk et al., 2010), demonstrating that emotion regulation and emotion generation regions indeed increase their synchronicity during the process of reappraisal. A recent meta-analysis confirmed this on a broader scale, putting forward a model in which ventrolateral PFC gives information to the dorsolateral PFC about the need to regulate, after which dorsolateral PFC carries out the regulation and relays the signals to the parietal and motor areas, as well as to the amygdala and the basal ganglia (Kohn et al., 2013). Focusing on connectivity changes within and between networks, another study similarly identified significant changes in connectivity among the visual, dorsal attention, frontoparietal and default mode networks during emotion regulation (Sripada et al., 2014).

1.1.4 Individual Differences in Reappraisal

Even though reappraisal is successfully used by many of us in our everyday lives, highly relevant individual differences have been noted in reappraisal ability across the population (McRae, Jacobs, Ray, John, & Gross, 2012; Troy, Shallcross, Davis, & Mauss, 2013; Troy, Wilhelm, Shallcross, & Mauss, 2010). A recent study systematically investigated the relationship between reappraisal ability, the

frequency of reappraisal use in everyday life, well-being, and several cognitive control processes (McRae et al., 2012). They reported a significant positive association between reappraisal ability, reappraisal frequency, the person's well-being, as well as the cognitive abilities of working memory capacity and set-shifting costs (McRae et al., 2012). Another study looking at individual differences in reappraisal ability showed that at high levels of stress, a better reappraisal ability might protect the person against depressive symptoms (Troy et al., 2010). By demonstrating the relevance of reappraisal ability for one's general well-being and resistance against psychopathology, the two studies demonstrate the importance of incorporating individual differences in reappraisal ability in the study of emotion regulation.

A number of neuroimaging studies have already examined the relationship between either neural activity or connectivity change during regulation and reappraisal ability. A few studies reported a positive association between the rate of activity increase in the PFC with emotion regulation and reappraisal ability (Ochsner et al., 2002; 2004; Phan et al., 2005; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008). Another study showed a positive relationship between amygdala activity decrease during reappraisal and reappraisal ability (Ochsner et al., 2004). A further study demonstrated a positive correlation between self-reported negative feelings and functional connectivity increase between amygdala and orbitofrontal cortex, as well as amygdala and dorsomedial PFC (Banks et al., 2007). Lastly, two studies examined the pathway supporting emotion regulation using mediation analysis, to assess whether the change in negative feelings, reflected in the reappraisal ability, was the consequence of the impact of prefrontal control systems on subcortical emotion generation systems (Kober et al., 2010; Wager et al., 2008). The first study found that the impact of ventrolateral PFC activity on reappraisal success was indeed mediated by amygdalar and ventral striatal brain activity (Wager et al., 2008). The second study found that the impact of dorsolateral PFC activity on reappraisal success was mediated by the ventral striatal activity (Kober et al., 2010).

1.2 Emotion, Motivation and Prediction Errors

Emotions are not simply reactions to our internal and external environments. They motivate our actions in a way that we strive to experience positive and avoid negative experiences (Izard, 2009; Lang & Bradley, 2010; LeDoux, 2012). The current section: a) introduces the motivational aspect of emotions; b) presents the neural network thought to support motivated behaviour; c) introduces prediction errors; d) describes the neural correlates of prediction errors; and e) reviews the few studies touching on the regulation of prediction errors.

1.2.1 The Motivational Aspect of Emotions

Emotion is a complex and multifaceted concept, so much so that researchers have yet to agree on its definition (Izard, 2010; LeDoux, 2012). In the traditional view, including that of emotion regulation, emotions are primarily viewed as responses or reactions to events in our internal and external environments (Ochsner et al., 2012). However, most researchers nowadays would agree that emotions are more than reactions to stimuli (Izard, 2010). One critical aspect of emotions, greatly emphasized in certain theoretical views, is their motivational significance (Izard, 2009; Lang & Bradley, 2010). Since emotional responses help determine the nature of a certain event or stimulus, in the simplest terms whether it is positive or negative, they are able to motivate our actions, in order to approach positive and avoid negative experiences (Lang & Bradley, 2010). Emotional events indeed attract our attention and are typically better remembered than non-emotional ones (Dolcos, Iordan, & Dolcos, 2011). Enhanced memory for emotionally significant events enables us to be better able to predict such events in the future were they to re-occur, which is the basis of associative learning (Dolan, 2002). The simplest type of associative learning is Pavlovian or classical conditioning, where a neutral stimulus acquires emotional significance (thereby becoming the conditioned stimulus) when paired with an emotionally relevant stimulus (called unconditioned stimulus) on a few occasions (Dolan, 2002; Schultz & Dickinson, 2000; Seymour & Dolan, 2008). Pavlovian conditioning thus embodies the motivational significance of emotions and provides a structured framework in which one can study emotions as more than simply reactions to significant events in our environment (LeDoux, 2012; Seymour & Dolan, 2008).

1.2.2 The Neural Network supporting Motivated Behaviour

Models outlining motivated behaviour are largely founded on animal research, and are often constructed with associative learning models in mind (Grace, Floresco, Goto, & Lodge, 2007; Pennartz et al., 2009; Pennartz, Ito, Verschure, Battaglia, & Robbins, 2011; Sesack & Grace, 2010). With regard to the neural network involved in motivated behaviour, the models emphasize ventral striatum as an integration centre that links motivational drives represented by limbic regions on the one hand, and motor control circuits that enable goal-directed behaviour on the other hand (Grace et al., 2007; Pennartz et al., 2009; Sesack & Grace, 2010). Ventral striatum is known to receive signals from several regions, including the PFC, hippocampus, amygdala and ventral striatum. Hippocampus provides spatial and contextual information, amygdala relays emotional drive and conditioned associations, and PFC provides executive control by, for example, enabling the inhibition of responses and task switching (Grace et al., 2007; Sesack & Grace, 2010). Ventral tegmental area, via dopaminergic input, is able to modulate both the activity in the ventral striatum, as well as the balance and integration of other inputs into ventral striatum, and thus has a direct influence on goal-directed behaviour (Grace et al., 2007; Sesack & Grace, 2010). In the framework of associative learning models, dopaminergic signals in the ventral tegmental area represent prediction errors, parameters that drive the process of learning (Pennartz et al., 2009).

1.2.3 Prediction Errors

In basic terms, learning involves making predictions of what might happen, experiencing the outcome, and adjusting predictions for the future, based on the errors of previous predictions (Ouden, Kok, & de Lange, 2012; Schultz & Dickinson, 2000). For instance, imagine you see a lightning and a moment later, rain starts to fall. The next time you see a lightning, you might immediately take out your umbrella and open it, predicting the rain. If the rain indeed starts to fall, your prediction was correct, strengthening the association between lighting and rain. However, if the raining does not start, you made a prediction error (i.e., you predicted the falling of rain but no rain came), and you will probably adjust your prediction of rain following lightning in the future. This type of associative learning, driven by prediction errors, is called Pavlovian or classical conditioning and one of

the most basic and fundamental models accounting for Pavlovian learning is the Rescorla Wagner model (Pearce & Bouton, 2001; Rescorla & Wagner, 1972; Schultz & Dickinson, 2000). The model accounts for three parameters of learning: prediction P, prediction error PE and learning rate λ (Rescorla & Wagner, 1972; Schultz & Dickinson, 2000). In an experimental setting, where the experiment consists of several trials, a prediction error is calculated as the difference between the prediction of the current trial P(t) and the actual outcome of the current trial R(t):

$$PE(t) = R(t) - P(t)$$

Prediction for the next trial P(t+1), on the other hand, is calculated by adding the prediction of the current trial P(t) and the prediction error of the current trial PE(t), the latter weighted by the learning rate λ (λ < 1):

$$P(t+1) = P(t) + \lambda PE(t)$$

Since predictions are re-evaluated based on prediction errors, prediction errors are seen as the driving force of learning (Rescorla & Wagner, 1972; Schultz & Dickinson, 2000). Learning rate, on the other hand, reflects the speed of learning, such that when the learning rate is high (for instance, λ = 0.9), a prediction error has a stronger effect on the next prediction. In the example above, this would mean that the absence of rain following lighting on one occasion would remove the prediction of rain on the next occasion. On the other hand, when the learning rate is low (for instance, λ = 0.1), learning is slower, and so prediction for the next occurrence takes several previous experiences into account. In the example above, the absence of rain on one occasion would only slightly reduce the expectation of rain for the future, but would not reverse it, especially if we have previously encountered the association between lighting and rain on several occasions.

1.2.4 The Neural Underpinnings of Prediction Errors

A number of studies have investigated the neural correlates of associative learning-related prediction errors in the human brain (for reviews, see Delgado, Li, Schiller,

& Phelps, 2008; Garrison, Erdeniz, & Done, 2013; Ouden et al., 2012). In the framework of motivational or associative learning, there are two different kinds of prediction errors; reward prediction errors are those pertaining to positive events, while aversive prediction errors are errors related to aversive outcomes. Both reward and aversive prediction errors can be positive (i.e., no expectation of outcome, but the reward or punishment is presented) or negative (i.e., expectation of outcome, but the reward or punishment is absent) (Delgado et al., 2008). In human neuroimaging studies, reward prediction errors have repeatedly been shown in the striatum, especially ventral striatum (Delgado et al., 2008; Garrison et al., 2013; Ouden et al., 2012). Aversive prediction errors, on the other hand, have been observed in the ventral striatum, ventral tegmental area, insula and amygdala (Garrison et al., 2013; M. Menon et al., 2007; Metereau & Dreher, 2013; Robinson, Frank, Sahakian, & Cools, 2010; Schiller, Levy, Niv, LeDoux, & Phelps, 2008; Seymour, Daw, Dayan, Singer, & Dolan, 2007; Seymour et al., 2004; Spoormaker et al., 2011).

1.2.5 The Regulation of Prediction Errors

Firstly, associative learning embodies the motivational aspect of emotions (LeDoux, 2012; Seymour & Dolan, 2008); secondly, prediction errors are thought to drive associative learning, including Pavlovian conditioning (Rescorla & Wagner, 1972; Schultz & Dickinson, 2000). Therefore, a good way to incorporate the motivational aspect of emotions into the concept of emotion regulation would be to test whether emotion regulation can extend beyond the modulation of emotional responses to additionally affect prediction error-related brain signals. A few existing studies have given clues as to whether and how prediction errors might be modulated. On the one hand, recent studies have shown that emotions themselves can modulate prediction error-related brain activity and thus directly influence learning (Katahira et al., 2015; Watanabe, Sakagami, & Haruno, 2013). If emotions can modulate neural prediction error-related activity and emotion regulation can affect emotions, emotion regulation is very likely to also modulate prediction errors. On the other hand, two recent studies found that a change in an emotional state was able to affect prediction error signals in the ventral striatum. The first study demonstrated that self-initiated reappraisal was able to modulate an aspect of the reward prediction

error coding in the right ventral striatum (Staudinger, Erk, Abler, & Walter, 2009). The second study showed that an increase in stress levels enhanced aversive (but not reward) prediction error-related activity in the right ventral striatum (Robinson, Overstreet, Charney, Vytal, & Grillon, 2013). It should be noted that both studies specifically analysed changes in the ventral striatum and overlooked other brain areas whose prediction error-related activity might also have been affected.

1.3 Social or Interpersonal Emotion Regulation

It is often underemphasized that our emotions are not only regulated by us, but can also be influenced by others around us. On the one hand, the mere presence of a supporting other can ameliorate our negative state; on the other hand, another's words can be even more effective at comforting us when we are feeling down (for reviews on social/interpersonal emotion regulation, see Reeck, Ames, & Ochsner, 2015; Zaki & Williams, 2013). This section introduces a) the modulation of emotions by the presence of others and neural systems supporting this effect; and b) the social or interpersonal emotion regulation and its neural underpinnings.

1.3.1 The Social Modulation of Emotion

Social relationships are highly beneficial to our health, such that poor social relationships represent a mortality risk similar to that of smoking and other well-known risk factors of mortality (Holt-Lunstad, Smith, & Layton, 2010). One possible process through which social relationships may influence our health is by 'buffering' the negative effects of stressors (Cohen, Gottlieb, & Underwood, 2001). In line with this, Social Baseline Theory proposes that social relationships represent bioenergetic resources, such that social proximity of trusting others reduces risk and decreases effort levels for achieving various goals (Beckes & Coan, 2011; Coan, 2011; Coan & Sbarra, 2015). According to this framework, the social presence of trusting others represents the 'baseline state' of the brain, in which the individual naturally feels safer and calmer and does not need to be vigilant for potential threats (Beckes & Coan, 2011; Coan, 2011; Coan & Sbarra, 2015). Empirical studies have indeed demonstrated that the mere presence of another person in the face of adverse stimuli can modulate emotional responses, such that the negative affect is

down-regulated (Coan, Schaefer, & Davidson, 2006; Eisenberger, 2013; Eisenberger et al., 2011; Younger, Aron, Parke, Chatterjee, & Mackey, 2010).

Studies exploring the neural basis of social emotion modulation or social support are slowly accumulating. One study, for example, tested the effect of spouse or stranger handholding versus no handholding on the neural responses to the threat of shock (Coan et al., 2006). Holding the hand of either a stranger or your own spouse reduced threat-related activity in the anterior and posterior cingulate, the left supramarginal gyrus and the right postcentral gyrus. Spousal handholding additionally decreased threat-related activity in the dorsolateral PFC, the caudate and the superior colliculus (Coan et al., 2006). Two further studies tested whether perceived social support of a loved one (induced by seeing their photograph in contrast to seeing a photo of a familiar acquaintance or stranger) would affect neural activations related to painful stimulation (Eisenberger et al., 2011; Younger et al., 2010). The two studies found that being reminded of a loved one, who typically provides social support, reduced pain-related activity in a number of areas, including anterior and posterior insula and dorsal anterior cingulate, along with reducing the feeling of pain. Furthermore, viewing a loved one, in contrast to an acquaintance or stranger, increased activity in the ventromedial PFC and the posterior cingulate, regions that typically signal safety (Eisenberger et al., 2011; Younger et al., 2010). Using a different design, another study similarly demonstrated that social support in response to social pain due to social exclusion was related to a decrease of insula activity and an increase in medial PFC activity (Onoda et al., 2009).

1.3.2 The Social Regulation of Emotion

In contrast to the passive modulation of emotion due to the presence of another person, social or interpersonal emotion regulation refers to a goal-driven process in which one person regulates another person's emotions (Reeck et al., 2015; Zaki & Williams, 2013). In the framework of social emotion regulation, the conventional type of emotion regulation, in which one attempts to regulate one's own emotions, has been termed intrapersonal emotion regulation (Zaki & Williams, 2013). Social emotion regulation typically involves the regulator (i.e., the person causing

emotional changes in the other person) and the target (i.e., the person whose emotions are being influenced by the other person) (Reeck et al., 2015; Zaki & Williams, 2013). Furthermore, the social regulation of emotion can be initiated by either the regulator (called 'extrinsic' social emotion regulation) or the target (termed 'intrinsic' social emotion regulation) (Zaki & Williams, 2013). In parallel to intrapersonal emotion regulation, the regulator in social emotion regulation can use various regulatory strategies depending on the emotion generation stage the target is in, such as modifying the situation, deploying attention, using cognitive strategies or modulating behavioural responses (Reeck et al., 2015). For instance, since the presence of trusting others can modulate negative feelings (see section *1.3.1 The Social Modulation of Emotion*), the target can modify the situation by seeking the presence and/or contact of a loved one. Alternatively, the regulator might similarly use the situation modification strategy and ensure that the target is close to a loved one if they think that the target is distressed. This nicely demonstrates the interdependence of social emotion modulation and regulation; despite being a passive strategy on its own, social emotion modulation is often part of the social emotion regulation process (Reeck et al., 2015; Zaki & Williams, 2013). Another strategy that a regulator can use to regulate the target's emotions, highly relevant for both every day life and for psychotherapy, is reappraisal, a cognitive emotion regulation strategy. Here, the regulator tries to change the target's emotions by suggesting alternative interpretations for the negative emotion-triggering stimulus or situation. Besides being the most effective and healthy strategy of intrapersonal emotion regulation, it is also uniquely relevant for situations where the aversive stimulus cannot be avoided (Reeck et al., 2015).

Little is known about the neural underpinnings of social emotion regulation. Nevertheless, studies from various disciplines provide the basis for a well-informed model, which has recently been provided in a review on social emotion regulation (Reeck et al., 2015). In contrast to intrapersonal emotion regulation, the networks involved in social emotion regulation are expected to differ between the regulator and the target. The regulator likely recruits the cognitive control network involving parietal and PFC areas, which is also used for intrapersonal emotion regulation (Buhle et al., 2014; Ochsner et al., 2012). Additionally, the regulator is expected to

recruit three further networks: a) the mentalizing or social cognitive network, including the medial PFC, the precuneus and the temporo-parietal junction (TPJ), in order to understand the intentions of the target (Frith & Frith, 2011; Lieberman, 2006; Schilbach et al., 2012); b) the action identification system, involving the premotor cortex and the inferior parietal module, to evaluate the goals and beliefs of the target (Van Overwalle & Baetens, 2009); and c) the system for empathy, including the mid-cingulate and the insula, which helps the regulator to vicariously understand the target's emotions (Lamm, Decety, & Singer, 2011). The neural systems supporting social emotion regulation in the target, on the other hand, likely involve both the social cognitive network (i.e., medial PFC, precuneus and TPJ) (Frith & Frith, 2011; Lieberman, 2006; Schilbach et al., 2012) and the cognitive control network (i.e., dorsolateral, ventrolateral and dorsomedial PFC and superior parietal areas) (Buhle et al., 2014; Ochsner et al., 2012). Furthermore, the target should additionally engage brain regions linked with emotion generation (e.g., amygdala, insula, striatum and periaqueductal gray), whose activity is expected to decrease during social emotion regulation (Reeck et al., 2015).

1.4 Aims of the Thesis

The overarching goal of the current thesis was to extend the concept of emotion regulation. The main method employed during the projects was functional magnetic resonance imaging (fMRI). We combined a typical event-related analysis, which highlights locations of task-related activations, with a model-based analysis, which additionally provides insight into the underlying mechanisms related to specific activations. We aimed to extend emotion regulation both in terms of the *emotion* and the *emotion regulation* part of the concept. With regard to *emotion*, it is becoming increasingly clear that emotions entail a lot more than simple reactions to stimuli; emotions can be motivating and therefore promote associative learning (Izard, 2009; Lang & Bradley, 2010; LeDoux, 2012). However, neuroscience research has not yet appropriately incorporated this relevant aspect of emotions into theories of emotion regulation. Projects 1 and 2 of the current thesis incorporated the motivational aspect of emotions into emotion regulation in terms of value-based prediction errors and their neural implementation. With regard to

emotion regulation, it is important to note that emotions are not only regulated by us, but are often influenced and controlled by others around us (Reeck et al., 2015). However, cognitive and affective neuroscience has largely ignored the social regulation and modulation of emotion. Projects 3 and 4 of the current thesis investigated the effects and the neural underpinnings of these underestimated social regulation types.

To provide a more comprehensive view of emotion regulation and bridge the gaps in literature noted above, the current thesis focused on the following research questions:

1) Besides being able to supress aversive response-related activity, can cognitive emotion regulation also impact prediction error-related activity in the brain? The first project 's aim was to investigate whether intrapersonal cognitive emotion regulation could affect the brain signal for motivated behaviour – the prediction error signal – in the ventral striatum, the insula and the ventral tegmental area.

2) What is the impact of emotion regulation on the network of motivated behaviour centred on the ventral striatum, and what role do individual differences in reappraisal have in this effect? The second project of this thesis examined the influence of intrapersonal cognitive emotion regulation on prediction error-related connectivity of the ventral striatum, taking into account participants' reappraisal ability.

3) What are the neural correlates of social emotion regulation, particularly social reappraisal? The third project investigated the neural underpinnings of social reappraisal in the target, their specificity in relation to the network supporting intrapersonal reappraisal, and the relationship between social regulation success and participants' attachment security levels.

4) Does social emotion modulation affect distinct types of neural activity in different subregions of the human insula? The fourth and last project of the current thesis focused on the effect of supportive social presence, a form of

social emotion modulation, on two distinct types of emotional brain activity – emotional response- and aversive prediction error-related activity – in the left and right anterior and posterior insula parts, and the association of this effect with aversive learning.

The first two projects relate to the extension of *emotion*, while the second two extend the *emotion regulation* part of what is conventionally considered emotion regulation. Overall, the current thesis aimed to provide a revised and extended view of emotion regulation, and by taking this view into account, to offer new insights into the effects and the neural underpinnings of intrapersonal reappraisal, social reappraisal and social emotion modulation.

2

Project 1: Cognitive Emotion Regulation Enhances Aversive Prediction Error Activity While Reducing Emotional Responses

The current chapter includes a research article entitled "Cognitive emotion regulation enhances aversive prediction error activity while reducing emotional responses". The article showed, for the first time, that cognitive emotion regulation, besides reducing emotional responses and aversive response-related activity, also affects aversive prediction error-related activity in the ventral striatum, ventral tegmental area, insula and hippocampus, possibly via tegmental dopaminergic pathways. The manuscript was published in NeuroImage in 2015.

Contributions:

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The author of this thesis is the first author of the manuscript. **S.M.B.** and C.S., with the help of G.S. and C.Z., conceived the experiment. **S.M.B.** recruited and trained participants, and **S.M.B.** and X.X. together conducted behavioural and fMRI data acquisition. **S.M.B.** analysed behavioural and imaging data, with some help from X.X. and A.D., and under the supervision of A.W. and V.R. **S.M.B.**, supervised by C.S., wrote the manuscript, which was commented on and revised by L.S.

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Cognitive emotion regulation enhances aversive prediction error activity while reducing emotional responses

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ABSTRACT

Cognitive emotion regulation is a powerful way of modulating emotional responses. However, despite the vital role of emotions in learning, it is unknown whether the effect of cognitive emotion regulation also extends to the modulation of learning. Computational models indicate prediction error activity, typically observed in the striatum and ventral tegmental area, as a critical neural mechanism involved in associative learning. We used model-based fMRI during aversive conditioning with and without cognitive emotion regulation to test the hypothesis that emotion regulation would affect prediction error-related neural activity in the striatum and ventral tegmental area, reflecting an emotion regulation-related modulation of learning. Our results show that cognitive emotion regulation reduced emotion-related brain activity, but increased prediction error-related activity in a network involving ventral tegmental area, hippocampus, insula and ventral striatum. While the reduction of response activity was related to behavioral measures of emotion regulation success, the enhancement of prediction error-related neural activity was related to learning performance. Furthermore, functional connectivity between the ventral tegmental area and ventrolateral prefrontal cortex, an area involved in regulation, was specifically increased during emotion regulation and likewise related to learning performance. Our data, therefore, provide first-time evidence that beyond reducing emotional responses, cognitive emotion regulation affects learning by enhancing prediction error-related activity, potentially via tegmental dopaminergic pathways.

Introduction

Cognitive emotion regulation is a powerful way of modulating emotional responses (Gross, 2002; Ochsner et al., 2012). For example, lifting up a picnic blanket and surprisingly noticing a snake will induce fear, including increased heart rate, fearful feeling, and a flight tendency. However, cognitively reappraising the situation, for instance realizing that the snake is a blindworm and therefore not dangerous, will cool your fear down immediately. During cognitive emotion regulation, brain activity in areas critical for experiencing emotions such as amygdala, insula and striatum is reduced (in the case of down-regulation) by emotion regulation signals from a network of dorsolateral, dorsomedial, and ventrolateral prefrontal regions (Buhle et al., 2014; Kalisch, 2009; Ochsner et al., 2012; Phillips et al., 2008). Emotions, however, do not only provide the organism with fast, consistent responses and attitudes to stimuli in the environment. Due to their motivational significance, emotions are able to adapt our behavior by changing the subjective value of stimuli and encouraging association formations (Izard, 2009; Lang and Bradley, 2010; Lang and Davis, 2006; Nesse and Ellsworth, 2009). But if so, the question arises whether cognitive emotion regulation might not only affect emotional responses but also related learning processes. In terms of the above example, noticing that the snake is a blindworm (i.e., regulatory reappraisal) may interfere with fear-associated adaptions (i.e., learning).

According to computational models in associative learning theory, learning is driven by reinforcement prediction errors (e.g., surprisingly

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noticing the snake) (Pearce and Bouton, 2001; Rescorla and Wagner, 1972; Schultz and Dickinson, 2000). Neural correlates of both reward and aversive prediction errors have been repeatedly observed in the striatum, ventral tegmental area, and other brain areas (Delgado et al., 2008a; Garrison et al., 2013; Robinson et al., 2010; Spoormaker et al., 2011). Recent studies have shown that emotions can directly influence learning by modulating such prediction error activity (Katahira et al., 2015; Watanabe et al., 2013). Given that emotions can directly modulate neural prediction error activity, emotion regulation is very likely to also modulate aversive prediction errors. We therefore hypothesized that cognitive emotion regulation might not only affect aversive response-related brain activity, but also affect brain activity related to aversive prediction errors. More specifically, along the idea that cognitive emotion regulation increases control of aversive emotions, we hypothesized that cognitive emotion regulation also increases control of aversive learning. A potential mechanism for the increased control of learning might be an increase of prediction error-related brain activity. In a related example, moderate levels of stress, typically beneficial in aversive situations and therefore representing a form of emotion regulation, increased aversive prediction error-related signals in the striatum for emotional stimuli in a simple cognitive task (Robinson et al., 2013). We therefore hypothesized that cognitive emotion regulation would decrease brain responses related to aversive emotions, and increase aversive prediction error-related brain activity.

We used functional magnetic resonance imaging (fMRI) to analyze the effect of cognitive emotion regulation on aversive response- and aversive prediction error-related brain activity. A model-based fMRI analysis combined with an aversive classical conditioning paradigm allowed insight into both aversive response- and aversive prediction error-related blood-oxygenation-level-dependent (BOLD) activity, observed concurrently in a specific trial. With regard to emotional responses, we expected cognitive emotion regulation to decrease aversive response-related activity in emotional brain areas such as insula, amygdala, and ventral striatum, replicating previous studies (Ochsner et al., 2012; Phillips et al., 2008). With respect to prediction errors, we hypothesized that cognitive emotion regulation would increase aversive prediction error-related neural activity in regions previously associated with aversive prediction errors, such as striatum, insula and ventral tegmental area (Delgado et al., 2008a; Garrison et al., 2013).

Materials and methods

Participants

24 healthy young participants were assessed by the experiment (all females), with a mean age of 24.8 years (SD = 2.3). Data from 4 participants had to be excluded from analysis, due to excessive head movement (translation > 2 mm, rotation > 2°; N = 2) and poor behavioral performance (N = 2, see Behavioral measures section). Only females were tested to avoid previously reported differences in the processing and regulation of emotions between genders (McRae et al., 2008; Whittle et al., 2011). Written consent was obtained from all participants and the study was approved by the local ethics committee (Technische Universität München). All participants were right-handed native German speakers, had normal or corrected-to-normal vision, no history of neurological or psychiatric disorders, and reported no intake of psychotropic medication. They received a financial compensation for their participation after completing the experiment.

Paradigm

To investigate the effect of cognitive emotion regulation on emotional responses and learning, we conducted a model-based fMRI study in which the visual presentation of aversive stimuli was combined with classical conditioning and varying conditioned–unconditioned stimulus (CS–US) contingencies. The conditioning paradigm was adapted from a previous study (Gläscher and Büchel, 2005), with the critical difference of exchanging painful stimulation for aversive pictures. This was done to facilitate comparison with previous emotion regulation studies, the majority of which investigated the regulation of emotional responses elicited by pictures from the International Affective Picture System (IAPS) (Buhle et al., 2014; Ochsner et al., 2012). A previous study on emotion–cognition interaction similarly used IAPS pictures as aversive outcomes in a reinforcement-learning paradigm, to examine prediction error-related brain activity (Katahira et al., 2015). On each trial, one of two symbols (CS; blue square or yellow pentagon) was presented, after which an aversive IAPS picture (US) followed on a proportion of trials (Paired trials; otherwise a blank screen was presented: non-Paired trials). Participant's task was to predict the occurrence of a US after a particular CS (Fig. 1/A). The CS–US contingency systematically fluctuated throughout the experiment, forcing participants to constantly adapt their predictions (Fig. 1/B) (Gläscher and Büchel, 2005). Importantly, a reappraisal strategy of self-distancing (Kalisch et al., 2005; Ochsner et al., 2004; Walter et al., 2009) was employed in the experiment, with participants trying to regulate stimulus-evoked emotional reactions in the Distance condition, or passively observe the stimuli in the Attend condition. Conditioning was modeled by the prediction error-based Rescorla–Wagner rule (Rescorla and Wagner, 1972), resulting in the learning parameter of interest, aversive prediction error (Fig. 1/C). For a trial t, aversive prediction error aPE was calculated as a difference between the actual outcome $R(t)$ and the predicted outcome $aP(t)$ [$aPE(t) = R(T) - aP(t)$], while predicted outcome for the next trial $aP(t+1)$ was updated by adding aversive prediction error of the current trial $aPE(t)$ to $aP(t)$, weighted by a learning rate λ [$aP(t+1) = aP(t) + \lambda aPE(t)$].

Each trial started with a 1 s showing of a fixation cross, after which the Regulation Strategy ('Distance' or 'Attend') was presented for 2 s. This was followed by a CS (blue square or yellow pentagon), presented for 6 s (Fig. 1/A). Participants were asked to indicate (predict) via a button press in the first 3 s of CS presentation whether a negative picture or no picture would follow the CS. The US, presented for 6 s, was a negative picture from the International Affective Picture System (Lang et al., 1997), shown on 50% of the trials (Paired trials). The picture set was balanced for arousal and valence across Distance and Attend conditions (for details on the set of pictures used in the experiment, see Supplementary methods in the Supplementary material). Next, participants had 3 s to evaluate the intensity of emotion via a button press on a scale from −3 to 3 (increments of 1; set to 0 on each trial). The inter-trial interval lasted for 4 ± 2 s. Each participant completed both Distance (i.e., self-distancing) and Attend (i.e., attentively observing) run, with the run order counterbalanced across participants.

Contingency variation

The CS–US contingency varied throughout the experiment following a low-frequency sine wave function, with 1.75 and 1.5 cycles per experimental run for CS1 and CS2, respectively (Fig. 1/B) (Gläscher and Büchel, 2005). Two CSs were used, because overlapping two contingency variation patterns (as opposed to using a single one) helped ensure that participants could not easily recognize the overall contingency pattern and therefore kept on learning throughout the experiment (Gläscher and Büchel, 2005). To guarantee that each CS predicted US occurrence with a different probability at each time point, the phase between the two CS-related sine functions was shifted by 96°. Reinforcement probability was kept constant at 50% for the first 4% or 19% of the run, for CS1 and CS2, respectively, to reduce cognitive search for contingency structure (Gläscher and Büchel, 2005). Participants were told that the two symbols (whose assignment to a particular CS–US contingency was counterbalanced across participants) predicted US occurrence with different probabilities, and that they should keep in mind that these probabilities could change throughout the run.

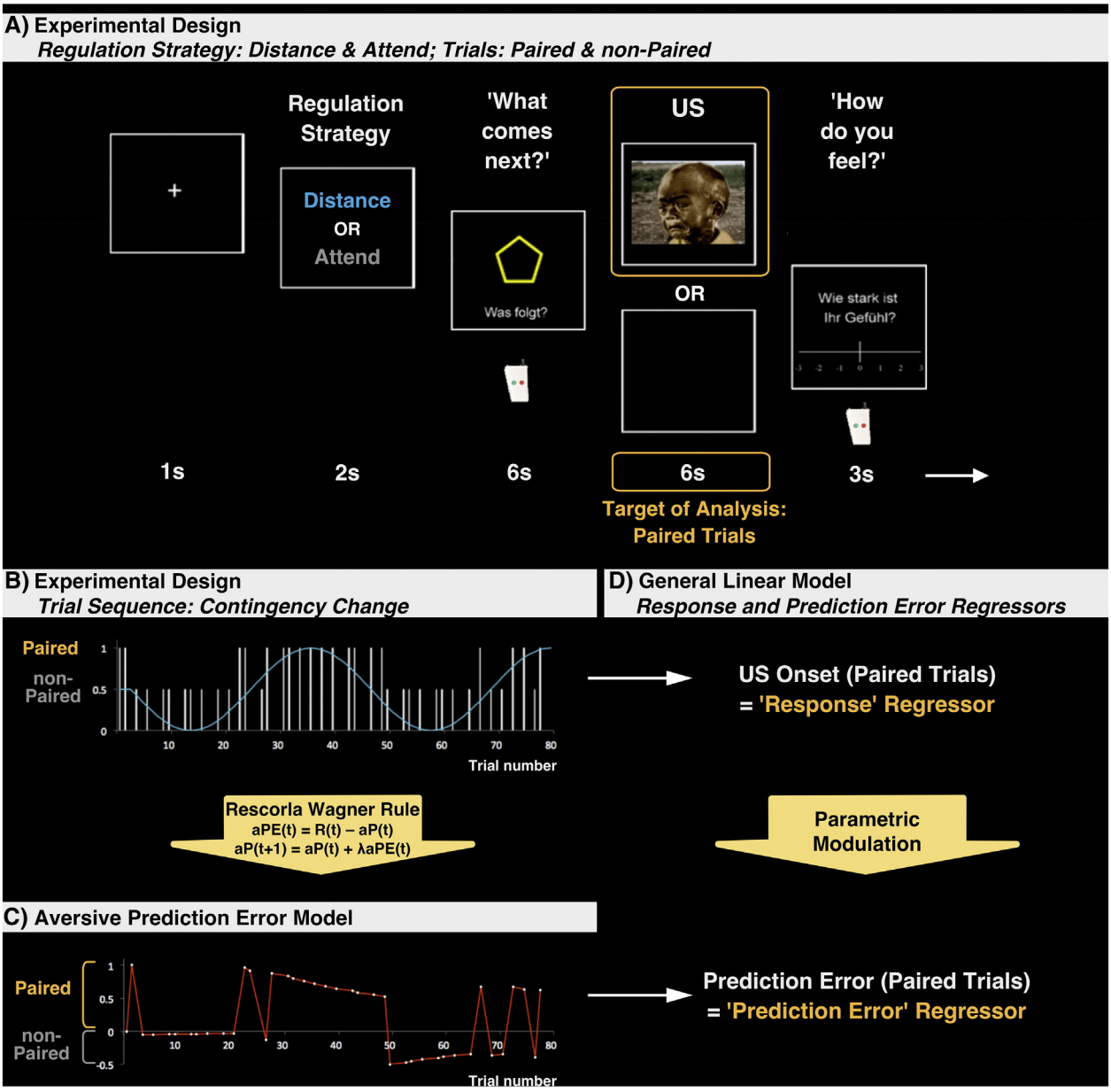

Fig. 1. Experimental design and aversive prediction error model for fMRI analysis. (A) Example of a trial. Trial types differed based on regulation strategy ('Distance' or 'Attend') and US presentation (Paired and non-Paired trials). A button press was required to predict whether a picture will follow or not, and at the end of the trial to indicate emotional feeling. (B) Contingency curve (based on a sine function, in cyan) and event train (stick function, in white) for one CS and one run are shown. (C) Model of aversive prediction error derived from the Rescorla Wagner rule was used as a parametric modulation of the US-onset regressor in the general linear model analysis. For a trial t, aversive prediction error aPE was calculated as a difference between the actual outcome $R(t)$ and the predicted outcome $aP(t)$ [$aPE(t) = R(T) - aP(t)$], while predicted outcome for the next trial $aP(t+1)$ was updated by adding aversive prediction error of the current trial $aPE(t)$ to $aP(t)$, weighted by a learning rate λ [$aP(t+1) = aP(t) + \lambda aPE(t)$]. CS — conditioned stimulus, US — unconditioned stimulus.

The experiment consisted of two runs (Distance and Attend) of 80 trials each, with an equal proportion (40 trials) of CS1 and CS2 trials in each run. A preudorandom CS event train was used, with the restriction that the same CS could not be presented on more than two consecutive trials (Gläscher and Büchel, 2005). An average reinforcement probability of 50% resulted in 40 Paired and 40 non-Paired trials in each run. Furthermore, to maximize similarity of CS1 and CS2, the two were followed by an equal number of Paired trials (i.e., 20 Paired and 20 non-Paired trials per CS in each run). To construct the trial sequence (stick function in Fig. 1/B), the two sine waves were used as threshold functions. A trial was Paired or non-Paired when a random number drawn from the amplitude range was below or above the threshold function, respectively (Gläscher and Büchel, 2005).

Emotion regulation instructions

In the Distance condition, participants were instructed to actively down-regulate emotions elicited by the negative pictures by means of cognitive self-distancing (Kalisch et al., 2005; Ochsner et al., 2004; Paret et al., 2011; Walter et al., 2009). They were given the option to use 'self-focused distancing' (e.g. 'The content of the images has nothing to do with me or my situation. I am not affected and none of my loved ones is affected.'), and/or 'reality-focused distancing' ('The pictures are not real, they are staged and have nothing to do with reality.'). In the Attend condition, participants were instructed to let the images passively sink in and to not alter the evoked emotions. They were told to attentively look at the presented picture, be aware of its meaning and to not change the triggered emotions.

Experimental procedure

Participants were instructed that they would participate in a functional imaging experiment investigating emotions and that they would learn a technique useful for modulating the impact of negative images on one's current emotional state.

After signing the consent form, they participated in a 20 min training session outside the scanner. Short 12-trial runs, analogous to the experiment but using unique IAPS pictures, were repeated until each participant was successful at both the learning and emotion regulation tasks. Prediction performance was measured by successful prediction of US occurrence as indicated via button press at the CS presentation. Regulation success, in turn, was verified via emotional intensity rating scores at the end of each trial and verbal reports of the exact emotion regulation strategy participants had used. All subjects were successfully trained at both emotion regulation and prediction tasks before continuing with the experiment.

Next, they completed the fMRI session, consisting of 2 runs lasting 35 min each, with a structural scan of 5 min between the runs, allowing participants to rest. To confirm the use of regulation strategies, participants were asked to verbally repeat the types of sentences they had used for both Distance and Attend conditions in the experiment. All participants complied with the experimental instructions.

Behavioral measures

For a behavioral measure of regulation success during scanning, participants rated their emotional feeling at the end of each run via a button press (on a scale of −3 to 3 in increments of 1; set to 0 on each trial). A 2 × 2 analysis of variance (ANOVA) on intensity rating scores with factors Regulation Strategy (Distance, Attend) and Trial Type (Paired, non-Paired) revealed a significant Regulation Strategy & Trial Type interaction ($F = 63.95$, $p < 0.001$), with a non-significant non-Paired-Distance versus non-Paired-Attend planned t-test ($t = 1.15$, $p > 0.26$). This confirmed the assumption that participants used the strategy of distancing chiefly when presented with negative pictures. Only Paired trials were therefore considered for the analysis of emotional intensity scores. Correspondingly, aversive prediction error-related fMRI analysis likewise focused on Paired trials only. Regulation success was calculated as a difference in intensity rating scores between Distance and Attend conditions for each participant.

To account for behavioral learning, participants also predicted US occurrence via button press (binary yes/no task) during the first 3 s of CS presentation in the scanner. For a measure of prediction performance, behavioral predictions were correlated with the actual US presentation sequence for each participant resulting in Pearson's r values, z-transformed for comparison across participants. Baseline performance (if one was to respond randomly) equaled 0. Only participants whose performance was significantly different from 0 in both Distance and Attend conditions were included in the analysis (2 participants were excluded due to poor performance). A second measure of learning was reaction times related to the prediction task. Participants were not given specific instructions regarding response speed, with the exception that they had to respond within the first 3 s of the CS being presented.

For analysis of behavioral data the three measures of prediction performance, reaction times and intensity rating scores were subjected to paired t-tests, comparing Distance and Attend conditions.

Functional MRI acquisition and preprocessing

All measurements were performed on a 3 Tesla Siemens scanner at the Klinikum rechts der Isar, Technische Universitaet Muenchen. Visual stimuli, presented with the Presentation software (Neurobehavioral Systems), were rear-projected on a screen at the head of the scanner and could be seen by participants through an adjustable mirror, mounted to a standard head coil. Presentation software also received trigger pulses signaling the beginning of each volume acquisition from the scanner.

Anatomical images were acquired with the magnetization-prepared rapid acquisition gradient echo (MPRAGE) T1-weighted sequence (1 × 1 × 1 mm resolution), and functional scans with the contrast-gradient echo-planar T2*-weighted sequence with a repetition time of 2 s, echo time of 30 ms, flip angle of 90°, acquisition matrix of 64 × 64, 35 slices, each 3 mm thick, with a gap of 0.6 mm, and an in-plane resolution of 3 × 3 mm.

Preprocessing and analysis of imaging data were carried out with SPM8 (Wellcome Department of Cognitive Neurology, London, UK). The T2*-weighted functional images were slice-timed, then realigned to the first image of the first run (after discarding the first two volumes) and unwarped. T1-weighted structural images were coregistered to the functional images, segmented and then normalized to a standard T1 template in the Montreal Neurological Institute (MNI) space with a 1 × 1 × 1 mm resolution. Normalization parameters from the latter were used to normalize the functional images, which were then resampled to 3 × 3 × 3 mm, smoothed with an 8 mm full-width-at-half-maximum Gaussian filter, and temporally high-pass filtered with a cut-off of 128 s.

Aversive PE model

Aversive predictions and aversive prediction errors were computed based on the Rescorla Wagner rule (Rescorla and Wagner, 1972). For a trial t, aversive prediction error aPE was calculated as a difference between the actual outcome $R(t)$ and the predicted outcome $aP(t)$:

$$aPE(t) = R(t) - aP(t) \times U(t).$$

In turn, predicted outcome for the next trial $aP(t+1)$ was updated by adding aversive prediction error of the current trial $aPE(t)$ to $aP(t)$, weighted by a learning rate λ:

$$aP(t+1) = aP(t) + \lambda aPE(t) \times U(t+1).$$

Parameter R was set to 1 when the aversive picture was delivered, and to 0 when no picture was shown. In turn, parameter U was used to disentangle CS1 and CS2 trials. Specifically, to calculate aP and aPE values related to CS1, U was set to 1 on CS1 trials, and to 0 on CS2 trials, and vice versa for the calculation of aPs and $aPEs$ related to CS2 (Gläscher and Büchel, 2005).

We used an optimized subject- and run-specific learning rate λ, derived from behavioral prediction scores. In detail, for each subject, separately for each CS and each run, subject's prediction responses were compared with the modeled aP values from the above Rescorla Wagner equation. Root-mean-square deviation (RMSD) was calculated for a range of learning rates from 0.001 to 1, in increments of 0.001. Best-fit learning rate for a specific CS, run and subject was determined by the associated global RMSD minimum. The mean best-fit learning rate across participants and conditions was 0.054 (SD = 0.031), which is consistent with previous studies (Gläscher and Büchel, 2005; den Ouden et al., 2009). A 2 × 2 ANOVA with factors Regulation Strategy (Distance, Attend) and CS (CS1, CS2) confirmed that mean learning rate did not differ across conditions (non-significant main effects and interaction, $F < 0.48$, $p > 0.49$).

fMRI data analysis

General linear model-based statistical analysis with the following regressors was carried out: a) hemodynamic response function-convolved onsets of CS1, CS2, US-Paired, US-non-Paired, Regulation Instruction, and Emotional Intensity Scale; b) aP and aPE values derived from the Rescorla Wagner rule as parametric modulations of the onset regressors:

aversive prediction 1 and aversive prediction 2 as parametric modulations of CS1 and CS2 onsets, respectively, plus aversive prediction error-Paired and aversive prediction error-non-Paired as parametric modulations of US-Paired and US-non-Paired onsets, respectively; and c) 6 movement regressors derived from realignment as regressors of no interest.

Activation analysis

To check for the main effects of two factors Regulation Strategy (Distance, Attend) and Trial Type (Paired, non-Paired) on aversive response-related activity without the impact of parametric modulation regressors, we first carried out a first-level analysis with no parametric modulation regressors, followed by a second-level 2 × 2 flexible factorial analysis with factors Subject, Regulation Strategy and Trial Type.

Based on the assumption that distancing was chiefly utilized during US presentation (see also Behavioral measures section), and to be able to directly compare the effects of cognitive emotion regulation on aversive response and aversive prediction error activity, all further analyses focused on Paired trials only (Fig. 1/A). At the group-level, two paired *t*-test analyses were carried out, with parameter estimates related to either US-Paired (i.e., Response-Paired) or Prediction Error-Paired regressors used as dependent variables, comparing Distance and Attend conditions. Statistical threshold for all activation analyses was set to $p < 0.05$, corrected for multiple comparisons (family wise error [FWE]) at the cluster level, based on a height threshold of $p < 0.005$, using whole-brain as the volume of interest.

Psychophysiological interaction analysis

An additional psychophysiological interaction (PPI) analysis was carried out, based on the activation results. Specifically, a generalized form of PPI (McLaren et al., 2012) was used, with three prefrontal clusters from Response: Distance > Attend (i.e., regions involved in regulation) as seeds and a midbrain-masked overlap of Response: Attend > Distance and Prediction Error: Distance > Attend as the region of interest (ROI). All regressors of the localization model (i.e., the activation analysis reported above) were also entered into the PPI and the PPI regressors were orthogonalized to them, only capturing effects over and above the localized activations. The midbrain mask was taken from previous studies (Aron et al., 2004; Murray et al., 2008).

Results

Behavioral results

With regard to regulation success, cognitive emotion regulation significantly reduced emotional intensity ratings, validating the current emotion regulation paradigm ($t = 10.779$, $p < 0.001$; Table S1). With respect to prediction reaction times, participants were significantly slower in making predictions on US occurrence while regulating their emotions compared to the non-regulating condition, potentially suggesting higher cognitive load during the regulation condition ($t = 2.005$, $p = 0.0295$; Table S1). With regard to prediction performance, prediction performance mean (based on z-transformed Pearson's r-values) remained unchanged with regulation ($t = 0.01$, $p = 0.496$; Table S1), in line with previous results where heightened stress-levels failed to affect behavioral learning accuracy (Robinson et al., 2013).

Main effects fMRI analysis

The main effects fMRI analysis without parametric modulation regressors revealed a significant main effect of Trial Type for the contrast Paired > non-Paired (Fig. S1/A), and a significant main effect of Regulation Strategy for the contrast Attend > Distance (Fig. S1/B). Crucially, both interactions yielded significant and meaningful activations, indicating a differential influence of cognitive emotion regulation on aversive response-related activity on Paired and non-Paired trials (Figs. S1/C, D), further corroborating the behavioral result that cognitive emotion regulation was chiefly utilized during Paired trials (see Behavioral measures section). All further analyses therefore focused on Paired trials only.

The effect of cognitive emotion regulation on aversive response activity

We verified that the presented emotional pictures evoked a typical emotion-related activation pattern (Fig. S2/A), in line with previous studies (Lindquist et al., 2012). To assess whether cognitive emotion regulation was able to reduce the emotional brain activity, we inspected the contrast Response: Attend > Distance. Aversive response-related activity decreased during emotion regulation in a wide network of areas including the insula, ventral tegmental area, periaqueductal gray area, thalamus, striatum, parietal, visual and somatomotor cortices (Fig. 2/A1; Table S2), consistent with previous studies (Buhle et al., 2014; Ochsner et al., 2012). When correlating behavioral regulation success scores with the degree of activity reduction due to cognitive emotion regulation in the peak cluster from Response: Attend > Distance (encompassing visual cortex, ventral tegmental area, periaqueductal gray area, left insula and striatum and left somatomotor cortex), we found that higher regulation success was related to higher emotion regulation-related activity reduction in this cluster, $r = -0.394$, $p = 0.043$ (Fig. 2/A2). We controlled the last finding for the effects of potential outliers. Using a cut-off of 3 standard deviations for the regulation success scores, we could find no outliers and therefore proceeded with the analysis, including all data points. With a stricter cut-off of 2 standard deviations, one data point would have been outside the range (mean regulation success = 0.99, SD = 0.41, mean − 2 × SD = 0.17, regulation success of participant 12 = 0.03.). Nevertheless, excluding this participant would have resulted in a trend for a significant correlation between the behavioral regulation success scores and the degree of activity reduction due to cognitive emotion regulation in the peak cluster from aR: Attend > Distance ($p = 0.077$). Taken together, results indicate that cognitive emotion regulation indeed reduced emotional responses, as expected from previous studies (Ochsner et al., 2012; Phillips et al., 2008).

The effect of cognitive emotion regulation on aversive prediction error activity

Aversive prediction error-related activity pattern during the Attend session involved bilateral striatum (Fig. S2/B), as shown previously (Delgado et al., 2008a; Garrison et al., 2013). Most relevant to the focus of our study, to test whether cognitive emotion regulation indeed enhanced aversive prediction error-related brain activity, we examined the contrast Prediction Error: Distance > Attend. It revealed that cognitive emotion regulation increased aversive prediction error-related brain activity in the right ventral tegmental area, hippocampus, insula, and ventral striatum (Fig. 2/B1; Table S2). The opposite contrast Prediction Error: Attend > Distance, testing which brain regions decreased aversive prediction error-related activity during cognitive emotion regulation, revealed no significant activations, even at a liberal threshold (Table S2). We then examined whether the effects of cognitive emotion regulation on aversive prediction error activity were related to subject-specific prediction performance scores. Aversive prediction error-related activity increase during regulation was correlated with the prediction performance difference (between Distance and Attend conditions) for the entire cluster in the contrast Prediction Error: Distance > Attend, encompassing right ventral tegmental area, ventral striatum, hippocampus and insula ($r = -0.545$, $p = 0.006$, Fig. 2/B2), as well as for each of the sub-regions separately (Supplementary analysis and Table S3). The correlation pattern suggests, firstly, that aversive prediction error enhancement was related to prediction performance, and secondly, that those participants who had more difficulty predicting US occurrence during regulation showed a higher emotion regulation-related increase of aversive prediction error activity. Together, results

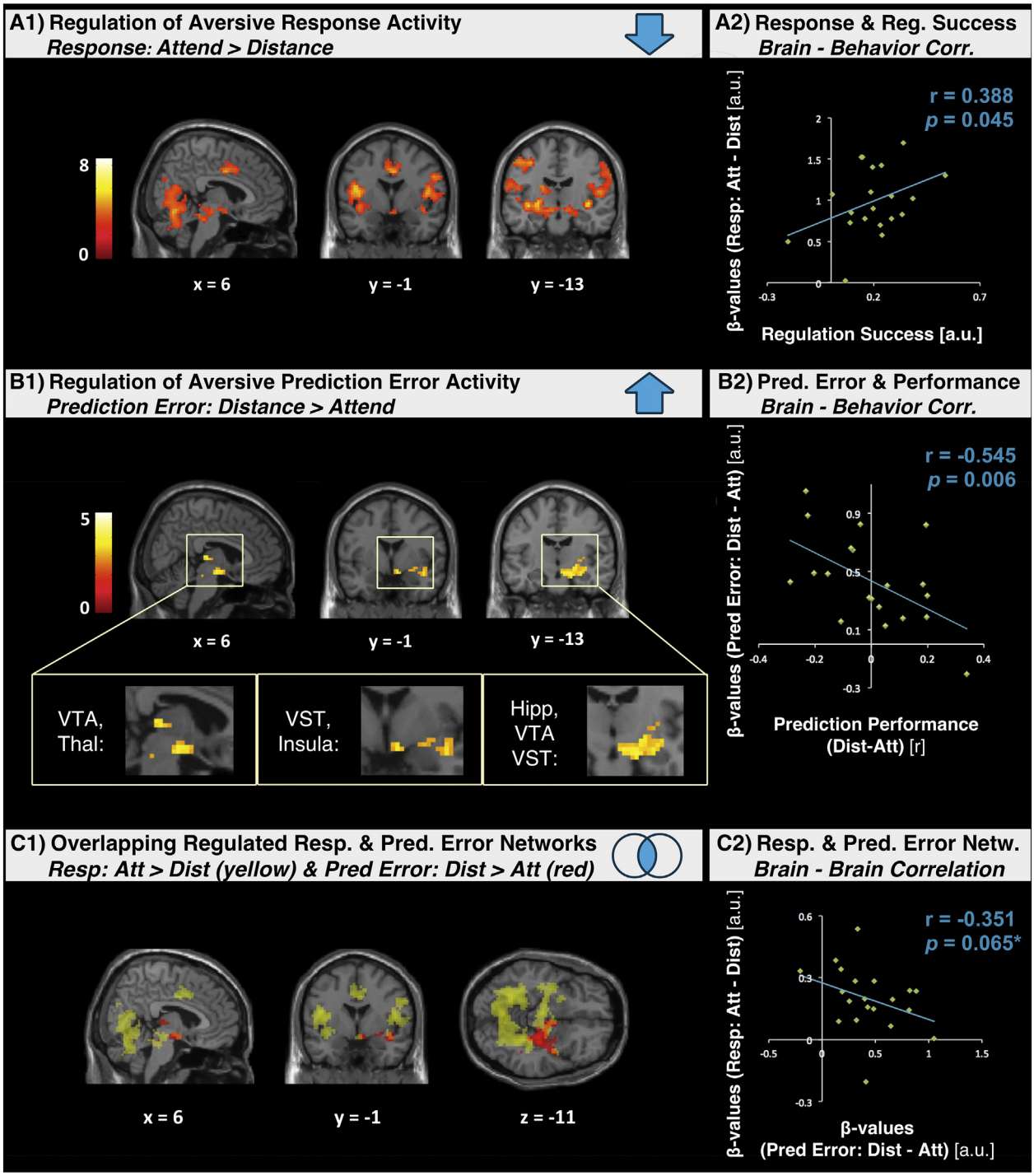

Fig. 2. The effect of cognitive emotion regulation on aversive response- and aversive prediction error-related activity. (A1) Cognitive emotion regulation reduced aversive response-related activity in the insula, ventral tegmental area, periaqueductal gray, thalamus, striatum, visual and somatomotor cortices. (A2) The higher the regulation success, the stronger the reduction in the peak Response: Attend > Distance cluster (encompassing visual cortex, ventral tegmental area and periaqueductal gray, left insula and striatum and left somatomotor cortex) across subjects. (B1) Cognitive emotion regulation increased aversive prediction error-related activity in the right ventral tegmental area, ventral striatum, hippocampus, thalamus and insula. (B2) The worse the prediction performance across subjects, the stronger the aversive prediction error-related increase of activity with emotion regulation in these areas. (C1) The overlap of aversive response and aversive prediction error networks regulated by cognitive emotion regulation. Contrast Response: Attend > Distance is shown in yellow and contrast Prediction Error: Distance > Attend is depicted in red. The two contrasts overlapped in the midbrain (including ventral tegmental area), hippocampus and insula. (C2) The effect of cognitive emotion regulation on aversive response- and aversive prediction error-related activity showed a trend for a negative correlation, such that the stronger the effect of emotion regulation on aversive response activity, the less aversive prediction error activity was affected, and vice versa (*a trend for significance). All contrasts were thresholded at $p < 0.05$, FWE cluster-corrected (with a height threshold of $p < 0.005$ and an extent threshold of 138 or 155 voxels for Response and Prediction Error analysis, respectively). a.u. — arbitrary units, r — Pearson's r, VTA — ventral tegmental area, Thal — thalamus, VST — ventral striatum, Hipp — hippocampus.

demonstrate that cognitive emotion regulation enhanced aversive prediction error-related signals in regions typical for aversive reinforcement learning (Delgado et al., 2008a; Goosens, 2011; Spoormaker et al., 2011), confirming the hypothesis that cognitive emotion regulation can indeed affect not only response-related but also learning-related brain activity.

Relationship between the regulation of aversive responses and aversive prediction errors

Considering our assumption that the regulation of emotional responses and learning is intimately connected, we tested whether the effects of cognitive emotion regulation on aversive response- and aversive prediction error-related activity were related to each other. We first examined regional overlap by overlaying the contrasts Response: Attend > Distance and Prediction Error: Distance > Attend. Indeed, the regulated aversive response and aversive prediction error networks overlapped in the midbrain (including ventral tegmental area), hippocampus and insula (Fig. 2/C1). Next, we looked for a quantitative relationship between the two effects across subjects. We found a trend for a significant negative correlation between the extracted beta-values, such that the stronger the effect of cognitive emotion regulation on aversive response activity, the less aversive prediction error activity was affected by emotion regulation, and vice versa (Fig. 2/C2; mean β-values of all significantly activated voxels in both contrasts were used). Together, results suggest that the effects of cognitive emotion regulation on emotional responses and learning are specifically interrelated in the ventral tegmental area, hippocampus, and insula.

Mechanism underlying the effect of cognitive emotion regulation

Finally, we sought to shed light on the neural mechanism by which emotion regulation might have influenced aversive prediction error-related brain activity. Firstly, the overlap of contrasts Response: Attend > Distance and Prediction Error: Distance > Attend (Fig. 2/C1), together with a trend towards a negative relationship between the effects of cognitive emotion regulation on aversive response and aversive prediction error activity (Fig. 2/C2), suggests that the effects of regulation might be linked with a common prefrontal system, whose activations are typically associated with regulatory activity (Buhle et al., 2014; Kalisch, 2009; Ochsner et al., 2012). Secondly, previous studies indicate that aversive prediction errors are coded by the salience-related midbrain dopaminergic neurons (Bromberg-Martin et al., 2010; Matsumoto and Hikosaka, 2009). Together with our findings, where ventral tegmental area was a part of the aversive prediction error-related neural network affected by regulation (see Fig. 2/B1), and given the evidence that the prefrontal cortex is able to directly modulate dopamine activity in the ventral tegmental area (Ballard et al., 2011; Gao et al., 2007; Gariano and Groves, 1988; Svensson and Tung, 1989), this implies that emotion regulation might be effective by directly targeting the source of the aversive prediction error signal in the ventral tegmental area.

To confirm this, we first identified regions involved in the regulation of emotions by examining the contrast Response: Distance > Attend. Replicating previous studies, a fronto-parietal network was revealed, including bilateral dorsolateral prefrontal cortex and left ventrolateral prefrontal cortex (Fig. 3/A; Table S2) (Buhle et al., 2014; Kalisch, 2009; Ochsner et al., 2012). We then performed three PPI analyses, using the three prefrontal clusters involved in emotion regulation as seeds. As mentioned above, cognitive emotion regulation was expected to enhance functional connectivity between a prefrontal regulatory cluster and the regulated midbrain ROI. The PPI analysis with a seed in the left ventrolateral prefrontal cortex revealed a significant connectivity-related activation in the ventral tegmental area for the contrast Response: Distance > Attend (MNI x, y, z: 3, −7, −11; $p < 0.05$, FWE small-volume corrected), suggesting an increased functional connectivity during cognitive emotion regulation between the left ventrolateral prefrontal cortex and ventral tegmental area (Fig. 3/B). The result was further corroborated by a significant correlation between the increase of functional connectivity between the ventrolateral prefrontal cortex and ventral tegmental area with cognitive emotion regulation and the prediction performance difference ($r = 0.386$, $p = 0.046$, Fig. 3/C). In line with the finding that an increase of ventral tegmental area activity during cognitive emotion regulation is negatively correlated with prediction performance (Fig. 2/B2), we found that the worse the participant was in predicting US occurrence during regulation, the more the connectivity between the ventrolateral prefrontal cortex and ventral tegmental area was enhanced during regulation. Together, results imply a relationship between the regulation of emotional responses and learning, pointing to a possible common source of regulatory activity in the ventrolateral prefrontal cortex and a common target of regulation in the ventral tegmental area.

Discussion

Cognitive emotion regulation has proven highly effective in modulating emotional responses (Delgado et al., 2008b; Kalisch et al., 2005; Ochsner et al., 2012). Results of the current study, however, show that cognitive emotion regulation is able to go beyond emotional responses and can also affect the mechanisms of emotional learning. Specifically, data demonstrate, for the first time, that while cognitive emotion regulation reduced aversive response-related activity in a wide network of areas, it increased aversive prediction error-related activity in an overlapping sub-network involving ventral tegmental area, ventral

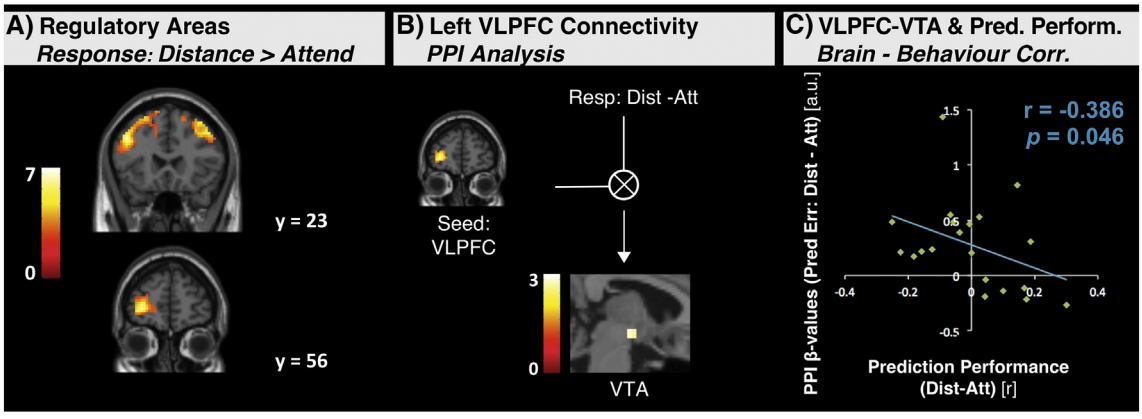

Fig. 3. The effect of cognitive emotion regulation on the ventrolateral prefrontal cortex–ventral tegmental area connectivity. (A) Cognitive emotion regulation-related activations included bilateral dorsolateral prefrontal cortex and left ventrolateral prefrontal cortex. The contrast was thresholded at $p < 0.05$, FWE cluster-corrected (with a height threshold of $p < 0.005$ and an extent threshold of 138 voxels). (B) PPI analysis revealed increased connectivity of the left ventrolateral prefrontal cortex cluster (taken from Response: Distance > Attend) with ventral tegmental area in the midbrain ROI, $p < 0.05$ FWE, small volume-corrected. (C) During emotion regulation, the worse the prediction performance across subjects, the higher the functional connectivity between the left ventrolateral prefrontal cortex and ventral tegmental area. PPI — psychophysiological interaction analysis, a.u. — arbitrary units, r — Pearson's r, VTA — ventral tegmental area, VLPFC — ventrolateral prefrontal cortex.

striatum, hippocampus and insula (Figs. 2/A1, B1). In addition, whereas the reduction of response activity was related to emotion regulation success, the enhancement of aversive prediction error-related activity was related to prediction performance (Figs. 2/A2, B2). Finally, a selective increase of functional connectivity during cognitive emotion regulation between ventral tegmental area and ventrolateral prefrontal cortex, a regulatory area, was likewise related to prediction performance (Fig. 3). Together, data suggest that cognitive emotion regulation may exert control over both emotional response- and learning-related brain activity.

Enhancement of aversive prediction error activity during cognitive emotion regulation

Emotional stimuli not only elicit emotional responses, but also prompt association formations to the surrounding neutral stimuli and thereby promote learning; specifically, emotions have been shown to modulate the learning parameter of prediction error (Izard, 2009; Katahira et al., 2011; Lang and Bradley, 2010; Nesse and Ellsworth, 2009; Watanabe et al., 2013). Cognitive emotion regulation, on the other hand, influences emotions; in particular, cognitive emotion regulation reduces aversive emotional responses and related brain activity (Fig. 2/A) (Buhle et al., 2014; Kalisch, 2009; Ochsner et al., 2012). Results of the current study demonstrate that cognitive emotion regulation can affect not only aversive emotional responses, but also the actual process of learning (Fig. 2/B). More specifically, we found that the regulatory technique of self-distancing increased aversive prediction error-related neural activity in the ventral striatum, hippocampus, and ventral tegmental area (Fig. 2/B1). Due to the overwhelming evidence from computational and empirical neuroscience for the essential role of prediction errors in associative learning (Delgado et al., 2008b; Garrison et al., 2013; Pearce and Bouton, 2001; Rescorla and Wagner, 1972; Schultz and Dickinson, 2000), our results indicate that cognitive emotion regulation influences learning-related neural processes in the context of emotions. Furthermore, we found that the aversive prediction error-related activity increase during regulation was related to the prediction performance difference (Fig. 2/B2), indicating that cognitive emotion regulation in fact affected the relationship between prediction performance change and aversive prediction error-related activity increase. In detail, during emotion regulation, the more a participant's prediction accuracy was lowered, the more aversive prediction error-related activity was enhanced, and opposite, the better the participant was in predicting during regulation, the less aversive prediction error-related BOLD activity was increased. A potential mechanism linking lower prediction performance with increased aversive prediction error activity during cognitive emotion regulation might be the learning rate parameter. In a recent study, using a reinforcement learning paradigm and an extended computational model of learning, a task-independent showing of a fearful face resulted in both an increased reward prediction error-related brain activity and a higher learning rate (Watanabe et al., 2013). Assuming that classical conditioning and reinforcement learning rely on similar mechanisms, participants with a lower learning performance might have increased their prediction error-related activity during emotion regulation by increasing the learning rate — the higher the learning rate, the higher the effect of prediction errors (Watanabe et al., 2013). Future studies, examining different types of learning combined with variable learning models could help further illuminate this effect.

In addition, given the role of prediction errors in attention allocation (Corlett et al., 2007; Fiorillo et al., 2003; Pearce and Hall, 1980), current results suggest that cognitive emotion regulation might enable us to enhance our attention to the relevant stimuli while decreasing aversive responses. Considering the importance of attention for memory (Chun and Turk-Browne, 2007), as well as the known link between cognitive emotion regulation and enhanced memory (Dillon et al., 2007; Hayes et al., 2010; Richards and Gross, 2000), emotion regulation-induced enhancement of the aversive prediction error activity may additionally result in an enhanced memory of the reappraised stimuli, especially those that are unexpected (i.e., for which the prediction error is high). Future studies might test this idea to see whether pictures associated with the highest prediction error values are indeed remembered better than those whose occurrence is expected.

Lastly, it is worth noting that a recent study showed an aversive prediction error-related signal increase in the ventral striatum with elevated stress levels induced by preparatory cues (Robinson et al., 2013), a seemingly incompatible finding. However, given that people tend to automatically down-regulate negative emotions in response to stress-related cues (Mauss et al., 2007; Phillips et al., 2008), the stressful condition in the study by Robinson and colleagues could have partially resembled the Distance condition in our study. Future work might help to disentangle the effect of stress and emotion regulation on aversive prediction errors.

Prediction error enhancement during cognitive emotion regulation in the ventral tegmental area

The network of areas whose aversive prediction error-related activity was enhanced during emotion regulation included the ventral tegmental area, a region previously associated with aversive prediction error coding in neuroimaging studies (Delgado et al., 2008a; Spoormaker et al., 2011). In terms of a neuromodulatory basis of aversive prediction errors, salience-coding dopaminergic neurons in the ventral tegmental area have been shown to activate in response to unexpected aversive events (Bromberg-Martin et al., 2010; Matsumoto and Hikosaka, 2009). Furthermore, acute intake of amphetamine, an indirect dopamine agonist, was shown to increase BOLD-related aversive prediction error signal in the ventral tegmental area and striatum in a previous study (Menon et al., 2007). Considering that emotion regulation in the current study targeted aversive prediction error-related activity in the ventral tegmental area, and given that prefrontal cortex has been shown to modulate dopaminergic ventral tegmental area activity (Ballard et al., 2011; Gao et al., 2007; Gariano and Groves, 1988; Svensson and Tung, 1989), cognitive emotion regulation might be affecting aversive prediction error-related activity by targeting the midbrain dopaminergic system. Indeed, an additional analysis confirmed that functional connectivity between one of the relevant regulatory regions – left ventrolateral prefrontal cortex – and ventral tegmental area increased with emotion regulation (Fig. 3/B), and that this connectivity increase was related to behavioral prediction performance (Fig. 3/C). Specifically, the worse the participant was in predicting US occurrence during cognitive emotion regulation, the more the connectivity between ventrolateral prefrontal cortex and ventral tegmental area was enhanced during regulation, mirroring the relationship between prediction performance and aversive prediction error-related activity change with cognitive emotion regulation (Fig. 2/B2). In detail, during emotion regulation, the more a participant's prediction accuracy was lowered, the more the connectivity between ventrolateral prefrontal cortex and ventral tegmental area was enhanced, perhaps to enable the participant to pay more attention to her errors, and opposite, the better the participant was in predicting during emotion regulation, the less the connectivity between ventrolateral prefrontal cortex and ventral tegmental area was increased, possibly because there was no need to pay that much extra attention to the errors. Together, our findings therefore suggest that cognitive emotion regulation-related effects on aversive prediction error activity might be moderated by dopaminergic ventral tegmental area pathways.

Prediction error enhancement during cognitive emotion regulation in the hippocampus, striatum and insula

Results further demonstrate that aversive prediction error-related activity was enhanced in the hippocampus, insula and ventral striatum

(Fig. 2/B1). The involvement of both striatum and insula is consistent with previous studies, where they have repeatedly been implicated as the neural correlates of aversive prediction errors (Delgado et al., 2008a; Metereau and Dreher, 2013; Robinson et al., 2010; Schiller et al., 2008; Seymour et al., 2004, 2007; Spoormaker et al., 2011). The strongest enhancement of aversive prediction error-related activity, however, was found in the right hippocampus (Fig. 2/B1; Table 2). Hippocampus has likewise been implicated in aversive learning and aversive prediction error coding (Goosens, 2011; Huh et al., 2009; Ploghaus et al., 2000). Furthermore, given the involvement of hippocampus in emotion regulation-related memory enhancement (Hayes et al., 2010), this result might further corroborate the link between cognitive emotion regulation-induced increase of aversive prediction error-related activity and memory enhancement.

Overlapping effects of cognitive emotion regulation on emotional response- and prediction error-related activity

The regulatory impact of cognitive emotion regulation on response- and learning-related activity overlapped in the ventral tegmental area, insula and hippocampus (Fig. 2/C1), suggesting that emotion regulation modulated regionally overlapping but partly distinct processes. Firstly, emotion regulation affected the two types of activity in opposite ways, such that aversive response-related activity was reduced (Fig. 2/A1), while the aversive prediction error-related activity was enhanced by regulation (Fig. 2/B1). Secondly, the two effects correlated with different behavioral measures, such that the reduction of response-related activity was related to regulation success (Fig. 2/A2), while the enhancement of aversive prediction error activity was related to prediction performance (Fig. 2/B2). Finally, the two effects showed a trend towards a negative correlation, such that an augmentation of one was related to a reduction in the other (Fig. 2/C2), suggesting that the effects of cognitive emotion regulation on emotional responses and learning might share cognitive resources. The results are in line with a number of previous studies demonstrating either emotional response- or aversive prediction error-related activity in the above-mentioned areas (Delgado et al., 2008b; Goosens, 2011; Lindquist et al., 2012; Spoormaker et al., 2011). Our data show that these processes are largely simultaneously and distinctively modulated by cognitive emotion regulation. Unfortunately, beyond a regional specification and direction of the effect, BOLD fMRI does not allow for further characterization of activity modulation. For example, due to a limited spatio-temporal resolution and an indirect measure of blood oxygenation changes, we cannot determine whether inhibitory GABA-ergic or neuromodulatory dopaminergic cell groups in the ventral tegmental area are modulated by cognitive emotion regulation. Future studies, for instance modulating dopamine levels, could be helpful for a further characterization of activity modulation by cognitive emotion regulation.

Other issues: limitations, amygdala, and clinical implications

The current study has some limitations. First, we did not find a significant effect of cognitive emotion regulation on behavioral learning (i.e., prediction performance). The missing effect of emotion regulation on learning at the behavioral level is in line with a previous study, where increased levels of stress failed to influence behavioral learning, while significantly affecting aversive prediction error-related neural activity (Robinson et al., 2013). The lack of cognitive emotion regulation-related influence on behavioral learning might be due to several reasons: a) the current study's model-based design focused on aversive prediction errors at a macroscopic brain level and not on learning at the behavioral level. As a consequence of this computational approach, the lack of a behavioral learning effect might be due to the lower sensitivity of behavioral prediction scores, for which the mean of all trials was used, based on a binary 'right' or 'wrong' answer. The computational model applied to the neural data, on the other hand, accounted for variations in the BOLD amplitude, based on the model's assumptions. b) The lack of performance difference might lie in the potentially higher cognitive load in the Distance condition, which is also reflected by a reaction time difference in prediction scores, such that participants took longer to respond during cognitive emotion regulation (Table S1). Nevertheless, this reaction time difference did not confound the effect of emotion regulation on either aversive response- or aversive prediction error-related activity, as was confirmed by an additional analysis, in which reaction time scores were included as a covariate. c) While no average-based effect of cognitive emotion regulation on prediction performance was found across subjects, we observed that the emotion regulation's effect on aversive prediction error-related activity was linked to subject-specific prediction performance scores (Fig. 2/B2). This brain-behavior relationship across subjects suggests an influence of further unknown factors that may confound the emotion regulation-related effects on learning, such as emotional response styles. Future studies may help illuminate these potential additional factors.

As a second limitation of the current study, the analysis did not focus on the effects of cognitive emotion regulation on prediction-related neural activity at the time of CS presentation. Such analysis was beyond the study's aim, which focused on directly comparing the effects of cognitive emotion regulation on emotional responses and learning.

Due to our whole-brain approach, we did not observe a modulating effect of cognitive emotion regulation on amygdala with regard to emotional responses, despite it being commonly affected by regulation in other studies (Buhle et al., 2014; Ochsner et al., 2012). An additional ROI-based analysis focused on amygdala for both aversive response- and aversive prediction error-related effects can be found in the Supplementary material (Supplementary analysis).

Our findings may have relevant clinical implications, particularly for affective disorders, which are characterized by impaired emotion regulation (Campbell-Sills and Barlow, 2007; Erk et al., 2010; Etkin and Wager, 2007; Johnstone et al., 2007). For example in major depression, both an inability of patients to reduce emotional responses to aversive stimuli (Campbell-Sills and Barlow, 2007; Johnstone et al., 2007) and a negative bias in attention, thinking and memory (Beck, 2008; Disner et al., 2011) are well-known; however, as yet, a possible interaction between impaired emotion regulation and negative bias is poorly understood. If aberrant response regulation were accompanied by failures in enhancing emotional learning for aversive stimuli, patients would be unable to boost their attention to errors, resulting in an unchanged pronounced negative bias typically seen in depressed patients. Future studies on patients with affective disorders could help test whether aberrant effects of cognitive emotion regulation on emotional learning are present in affective disorders.

Conclusion

In summary, we show that cognitive emotion regulation is able to reach beyond the reduction of emotional responses to directly affect the process of emotional learning by increasing aversive prediction error-related activity in the ventral tegmental area, striatum, hippocampus and insula, potentially via tegmental dopaminergic pathways. The result highlights a neglected dimension of emotion regulation, namely its impact on emotional learning.

Conflicts of interest

The authors declare no conflicts of interest, financial or otherwise.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2015.08.038.

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Supplementary material for

'Cognitive Emotion Regulation Enhances Aversive Prediction Error Activity While Reducing Emotional Responses'

by Mulej Bratec, S. et al.

Supplementary Methods

Supplementary Analysis

Supplementary Tables

Supplementary Figures

Supplementary Methods

Emotional Stimuli

To elicit aversive emotions, 80 negative pictures were selected from the International Affective Picture System (IAPS), and divided into two groups of 40 pictures, for use (in a counterbalanced way) in the two emotion regulation conditions (Distance and Attend), based on normative ratings of valence and arousal. Valence means for the two sets of IAPS pictures were 2.25 (SD = 0.48) and 2.15 (SD = 0.40), while arousal means equaled 6.05 (SD = 0.60) and 6.10 (SD = 0.61). T-tests confirmed that there was no significant difference between the two sets of pictures for either arousal ($p > 0.32$) or valence ($p > 0.68$). The picture presentation order was random and differed for each participant. Set 1 contained the following IAPS pictures: 3160, 9400, 9415, 9911, 9007, 3010, 3170, 9322, 3051, 9421, 9900, 6838, 3550, 6021, 6571, 3301, 2683, 9181, 3212, 8485, 6550, 6563, 3100, 9635.1, 2730, 2352.2, 3185, 6212, 9183, 3071, 2717, 3016, 9800, 9075, 3005.1, 1930, 3102, 2095, 6821, 9902, while set 2 contained the following pictures: 9420, 2799, 3064, 9908, 3266, 2053, 3061, 3500, 2691, 3080, 9250, 6830, 9571, 6315, 9940, 9433, 9428, 9903, 9941, 9006, 3030, 3350, 3261, 6300, 9326, 3000, 6560, 2703, 3168, 9252, 9405, 9332, 9043, 9300, 9560, 7380, 3017, 9570, 9254, 6230.

Supplementary Analysis

Aversive Prediction Error-Related Region of Interest-Based Correlation Analysis

The cluster resulting from the contrast Prediction Error: Distance > Attend spanned more than one anatomical region. In order to show which region(s) were driving the correlation effect (Figure 2/B2), we followed an anatomical region of interest (ROI)-based approach and divided the cluster into anatomical sub-regions hippocampus, striatum, insula and midbrain (based on 'wfupickatlas' from SPM8). After obtaining a difference score for each participant, indicating the strength of enhancement with cognitive emotion regulation (Distance – Attend), we performed correlations between BOLD difference scores in the sub-regions and prediction performance difference scores (Distance – Attend). All of the sub-regions exhibited a significant negative correlation with prediction scores, indicating that the result was highly consistent and uniform across the whole original cluster (Table S3).

The Effect of Cognitive Emotion Regulation on Aversive Response-Related Activity in the Amygdala

In line with previous studies, the presentation of negative pictures elicited amygdala-related activation (Figure S2/A) (Lindquist et al., 2012). However, based on a whole-brain analysis, cognitive emotion regulation failed to significantly affect this response-related activity in the amygdala. We therefore performed a ROI-based analysis focused on the anatomical amygdala ROIs, to determine whether cognitive emotion regulation suppressed responses in the amygdala, as suggested by previous studies (Buhle et al., 2014; Ochsner et al., 2012). We extracted average ß-values related to the Response regressor from the left and right anatomical amygdala ROIs and performed a t-test comparing Attend and Distance conditions. Results showed a trend for significance in the left amygdala (t = 1.575, p = 0.066), but no suppression of response-related activity in the right amygdala (t = 0.406, p = 0.345).

The Effect of Cognitive Emotion Regulation on Aversive Prediction Error-Related Activity in the Amygdala

Since amygdala has also been shown to code for aversive prediction errors (Boll et al., 2013; McHugh et al., 2014; Metereau and Dreher, 2013), we expected that cognitive emotion regulation might modulate this activity. However, we failed to observe prediction error-related amygdala activations in a whole-brain approach, and therefore performed an additional ROI-based analysis, based on anatomical amygdala ROIs, to test whether amygdala activations in our study were modulated by emotion regulation. We extracted average ß-values related to the Prediction Error regressor from the left and right anatomical amygdala ROIs and performed a t-test comparing Attend and Distance conditions. Results showed a trend for significance in the left amygdala (t = 1.482, p = 0.078), but no suppression of prediction error-related activity in the right amygdala (t = 1.018, p = 0.161). Together with response-related findings for amygdala above, results indicate that cognitive emotion regulation shows a trend towards suppressing aversive responses and aversive prediction errors in the amygdala. However, further studies are necessary to support this result.

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Supplementary Tables

Table S1. Behavioral measures.

Behavioral Measure	Emotional Intensity Rating (SEM)	Reaction Time (SEM)	Prediction Performance (SEM)
Attend	- 1.56 (0.09)	1.14 (0.04)	0.35 (0.03)
Distance	- 0.85 (0.1)	1.21 (0.05)	0.36 (0.03)
T-test: Attend vs. Distance	$p < 0.001$	$p < 0.05$	n.s.

A t-test on emotional intensity ratings showed that distancing significantly reduced negative feelings, a t-test on reaction time scores revealed a significant slowing during distancing, and a t-test on prediction performance scores showed no significant effects of cognitive emotion regulation. N.s. – non-significant, SEM – standard error of mean.

Table S2. Significant activations for the regulation of aversive response- and aversive prediction error-related activity.

Region activated	Hemisphere	Coordinates			Z value	Cluster size
		x	y	z		
Response: Distance > Attend						
Middle frontal gyrus	R	42	17	52	5.01	803
Middle frontal gyrus	L	-45	23	34	4.82	
Superior medial frontal gyrus	L	-3	38	37	3.89	
Inferior frontal gyrus	L	-51	17	22	3.59	
Superior frontal gyrus	L	-12	23	64	3.22	
Superior medial frontal gyrus	R	6	44	46	3.17	
Superior frontal gyrus	R	21	26	55	3.12	
Inferior parietal gyrus	L	-42	-52	40	4.46	430
Supramarginal gyrus	L	-60	-49	28	3.42	
Angular gyrus	R	57	-52	31	4.46	399
Middle frontal gyrus	L	-27	59	4	4.74	180
Response: Attend > Distance						
Supramarginal gyrus	L	-57	-28	34	5.40	5892
Middle occipital gyrus	L	-51	-70	1	4.80	
Fusiform gyrus	L	-24	-55	-14	4.64	
Middle temporal gyrus	L	-51	-67	10	4.58	
Middle temporal gyrus	R	51	-61	4	4.56	
Fusiform gyrus	R	30	-52	-17	4.46	
Insula	L	-39	-22	1	4.19	
Cerebellar vermis	R	0	-58	-29	4.15	
Postcentral gyrus	L	-42	-19	49	4.13	
Precuneus	R	24	-61	25	4.12	
Cuneus	R	21	-82	43	4.11	
Cerebellum	L	-6	-67	-11	4.10	
Middle occipital gyrus	R	39	-85	25	3.94	
Rolandic operculum	L	-36	5	13	3.93	
Caudate	L	-12	-7	16	3.91	
Periaqueductal gray	L	-3	-31	-17	3.90	
Precentral gyrus	L	-33	-13	49	3.84	
Putamen	L	-24	8	-8	3.67	
Cerebellum	R	24	-37	-23	3.66	
Lingual gyrus	L	-15	-79	-2	3.64	
Precuneus	L	-12	-55	13	3.52	

Hippocampus	R	30	-31	-8	3.45	
Lingual gyrus	R	15	-67	-8	3.44	
Superior temporal gyrus	L	-48	-10	4	3.39	
Cuneus	L	-9	-76	19	3.24	
Hypothalamus	R	3	-4	-14	3.22	
Calcarine fissure	R	15	-52	7	3.10	
Superior occipital gyrus	L	-18	-73	22	2.91	
Superior occipital gyrus	R	27	-73	43	2.77	
Parahippocampal gyrus	R	33	-28	-17	2.73	
Supramarginal gyrus	R	66	-19	31	4.70	1072
Insula	R	39	-16	-2	4.47	
Postcentral gyrus	R	51	-25	22	4.25	
Rolandic operculum	R	45	-1	10	3.85	
Superior parietal gyrus	R	18	-58	58	4.27	284
Midcingulate gyrus	R	15	-31	40	4.00	
Inferior parietal gyrus	R	33	-46	55	3.92	
Midcingulate gyrus	R	0	2	40	4.02	165
Prediction Error: Distance > Attend						
Hippocampus	R	24	-22	-11	4.11	432
Thalamus	R	9	-22	4	3.59	
Insula	R	42	-4	-17	3.44	
Midbrain (VTA/SN)	R	9	-10	-14	3.40	
Superior temporal gyrus	R	45	8	-20	3.27	
Fusiform	R	36	-37	-20	3.20	
Hypothalamus	R	-1	2	-14	3.19	
Putamen	R	30	-4	-8	3.04	
Cerebellum	R	30	-43	-26	2.92	
Thalamus	L	-9	-28	7	2.77	
Parahippocampal gyrus	R	21	-40	-8	2.76	
Periaqueductal gray	R	9	-25	-17	2.70	
Prediction Error: Attend > Distance						
No significant activations.						

Results are based on differential t-contrasts, thresholded at $p < 0.05$, FWE cluster-corrected, and a height threshold of $p < 0.005$. Some clusters cover more than one brain region; peak coordinates reflect local maxima. Coordinates conform to the Montreal Neurological Institute (MNI) space.

Table S3. Aversive prediction error-related region of interest-based correlation analysis.

Region	Whole cluster	Hippocampus	Striatum	Insula	Midbrain
Pearson's r	-0.545	-0.464	-0.389	-0.638	-0.520
Alpha	0.006**	0.020**	0.045**	0.001**	0.009**

Table shows correlation analyses between BOLD difference scores (Distance – Attend) in the indicated regions and prediction performance difference scores (Distance – Attend). As can be seen above, all of the sub-regions exhibited a significant negative correlation with prediction scores. ** - Significant at $p < 0.05$.

Supplementary Figures

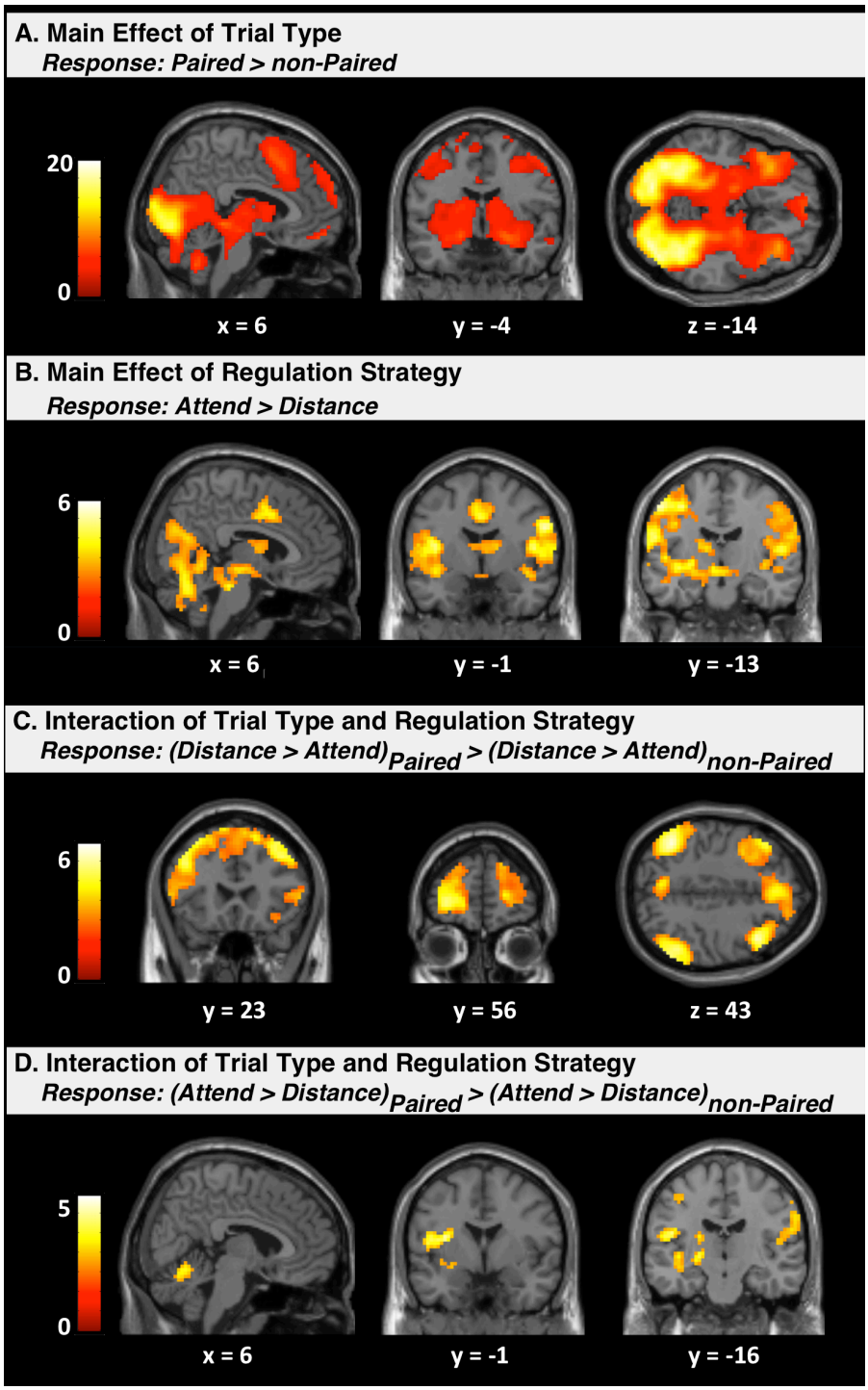

Figure S1. Main-effects fMRI analysis. (A) Activation pattern related to the main effect of Trial Type for the contrast Paired > non-Paired. (B) Activation pattern related to the main effect of Regulation Strategy for the contrast Attend > Distance. (C) Activation pattern related to the interaction effect between Trial Type and Regulation Strategy, for the contrast $(\text{Distance} > \text{Attend})_{\text{Paired}} > (\text{Distance} > \text{Attend})_{\text{non-Paired}}$. (D) Activation pattern related to the interaction effect between Trial Type and Regulation Strategy, for the contrast $(\text{Attend} > \text{Distance})_{\text{Paired}} > (\text{Attend} > \text{Distance})_{\text{non-Paired}}$. All contrasts were thresholded at $p < 0.05$, FWE cluster-corrected (with a height threshold of $p < 0.005$ and an extent threshold of 169 voxels).

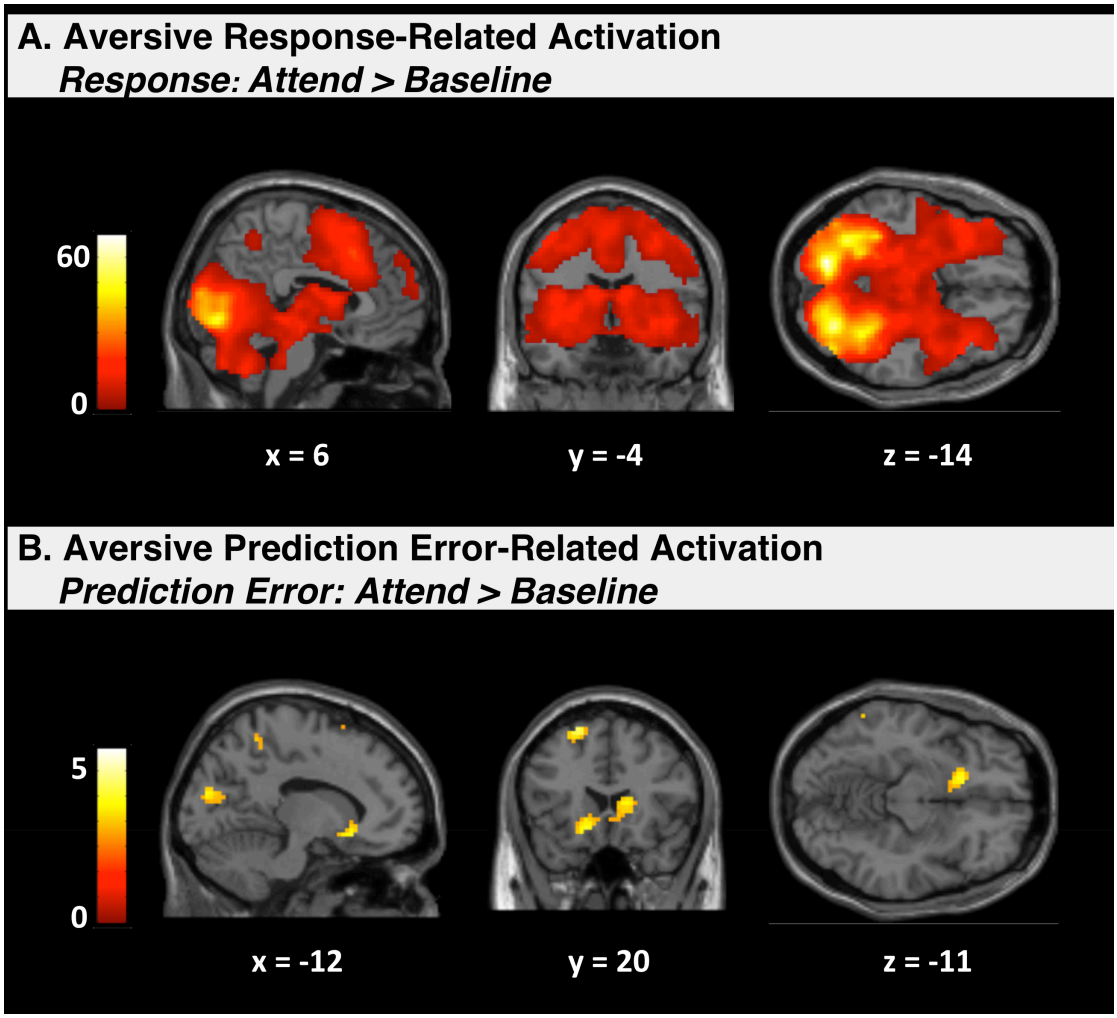

Figure S2. Aversive response- and aversive prediction error-related activation patterns. (*A*) Activation pattern related to the presentation of IAPS pictures (Response regressor). The contrast was thresholded at $p < 0.05$, FWE cluster-corrected (with a height threshold of $p < 0.005$). (*B*) Activation pattern related to the aversive prediction error (Prediction Error regressor). The contrast was thresholded at a height threshold of $p < 0.005$ and an extent threshold of 50 voxel.

3

Project 2: Cognitive Emotion Regulation Modulates the Balance of Competing Influences on Ventral Striatal Aversive Prediction Error Signals

The current chapter includes a research manuscript entitled "Cognitive emotion regulation modulates the balance of competing influences on ventral striatal aversive prediction error signals". It demonstrates, for the first time, that cognitive emotion regulation, when implemented by a person with high reappraisal ability, can affect the balance among competing striatal inputs to reduce the inputs coming from subcortical afferents, while maintaining the ones coming from the PFC. The manuscript is currently unpublished.

Contributions:

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The author of this thesis is the first author of the manuscript. **S.M.B.** and C.S., with the help of X.X., G.S. and C.Z., conceived the experiment. **S.M.B.** recruited and trained participants, and **S.M.B.** and X.X. together conducted behavioural and fMRI data acquisition. **S.M.B.** analysed behavioural and imaging data, with some help from X.X., Y.W. and A.W., and under the supervision of V.R. and C.S. **S.M.B.** wrote the manuscript, supervised by C.S., and the manuscript was commented on and revised by L.S.

Cognitive Emotion Regulation Modulates the Balance of Competing Influences on Ventral Striatal Aversive Prediction Error Signals

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Abstract

Cognitive emotion regulation (CER) is a critical human ability to face aversive emotional stimuli in a flexible way, via recruitment of specific frontal brain circuits. Animal research reveals a central role of ventral striatum in emotional behaviour, for both aversive conditioning, with striatum signalling aversive prediction errors (aPE), and for integrating competing influences of distinct striatal inputs from regions such as the prefrontal cortex (PFC), amygdala, hippocampus and ventral tegmental area (VTA). Translating these ventral striatal findings from animal research to human CER, we hypothesized that successful CER would affect the balance of competing influences of striatal afferents on striatal aPE signals, in a way favouring PFC as opposed to subcortical striatal inputs. Using aversive classical conditioning with and without CER during fMRI, we found that during CER, superior regulators indeed reduced the modulatory impact of subcortical striatal afferents (hippocampus, amygdala and VTA) on ventral striatal aPE signals, while keeping the PFC impact intact. In contrast, inferior regulators showed an opposite pattern. Our results demonstrate that ventral striatal aPE signals and associated competing modulatory inputs are critical mechanisms underlying successful cognitive regulation of aversive emotions in humans.

Introduction

Cognitive emotion regulation (CER) is a vital human ability to face aversive emotional stimuli in a flexible way (Buhle et al., 2014; Gross, 2002; Kalisch, 2009). Based on animal research, ventral striatum is critical for emotional behaviour, particularly for aversive conditioning, with striatum signalling aversive prediction errors (aPE), and for integrating competing modulatory influences from several regions such as the prefrontal cortex or medial temporal lobes (Grace, Floresco, Goto, & Lodge, 2007; Pennartz, Ito, Verschure, Battaglia, & Robbins, 2011). In humans, however, it is unknown whether ventral striatal aPE signals and their modulation are associated with successful CER.

Ventral striatum is widely known for its role in associative learning, particularly in Pavlovian conditioning (Grace et al., 2007; Liljeholm & O'Doherty, 2012; O'Doherty et al., 2004; Pennartz et al., 2011). It has been repeatedly implicated in aversive Pavlovian conditioning in a variety of human studies (Delgado, Jou, & Phelps, 2011; Jensen et al., 2003; Klucken et al., 2012; Robinson, Frank, Sahakian, & Cools, 2010). Based on computational models of associative learning theory, Pavlovian conditioning is driven by PEs (Liljeholm & O'Doherty, 2012; Pearce & Bouton, 2001; Rescorla & Wagner, 1972; Schultz & Dickinson, 2000), and a number of studies have demonstrated the encoding of aPEs (i.e., PEs related to aversive situations) by the ventral striatum during aversive Pavlovian conditioning (Garrison, Erdeniz, & Done, 2013; Menon et al., 2007; Robinson, Overstreet, Charney, Vytal, & Grillon, 2013; Seymour, Daw, Dayan, Singer, & Dolan, 2007; Seymour et al., 2004).

Emotions play an essential role in modulating or controlling behaviour (Cardinal, Parkinson, Hall, & Everitt, 2002; Lang & Bradley, 2010). Animal models of controlled motivated behaviour highlight the critical role of ventral striatal activity and its control by diverse competing afferent inputs (Floresco, 2015; Grace et al., 2007; Pennartz et al., 2011; 2009; Sesack & Grace, 2010). Specifically, ventral striatum is seen as an integration area, controlled by a number of afferent regions, including the prefrontal cortex (PFC), hippocampus, amygdala, and ventral tegmental area (VTA) (Fig. 1). PFC input into ventral striatum is thought to enable behavioural flexibility, hippocampal input to provide contextual and spatial

information, amygdala to support emotional behaviour, particularly cue conditioning, and dopaminergic input from VTA is suggested to modulate influences of the other afferents on ventral striatum, possibly via PE signals (Floresco, 2015; Grace et al., 2007; Pennartz et al., 2011). While VTA is also an output region of the ventral striatum, PFC, hippocampus and amygdala are its unidirectional afferents, providing input through direct anatomical connections (Floresco, 2015; Grace et al., 2007; Haber & Knutson, 2010; Sesack & Grace, 2010).

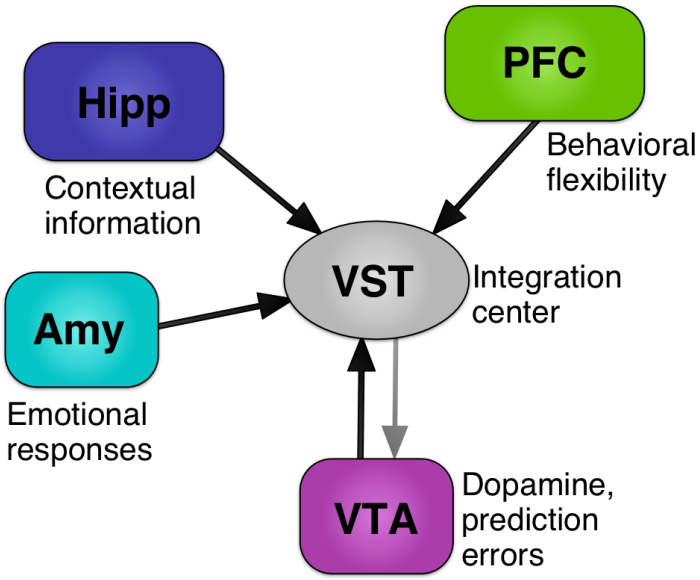

Figure 1. The model of motivated behaviour, adapted, with permission, from (Grace et al., 2007). In this model, ventral striatum (VST) is an integration centre, influenced by a number of afferent regions: PFC input into ventral striatum is thought to enable behavioural flexibility, hippocampal (Hipp) input to provide contextual and spatial information, amygdala (Amy) to support emotional behaviour, particularly cue conditioning, and dopaminergic input from VTA to modulate connections between other afferents and the ventral striatum, possibly via PE signals.

In the case of human emotional behaviour, characterized by both emotion adaption and emotion regulation, a similar neural network might be relevant. Particularly in the case of CER or reappraisal, the balance among ventral striatal inputs may shift in favour of PFC input, to realize behavioural flexibility in response to emotional stimulation. Indeed, previous functional magnetic resonance imaging (fMRI) studies in humans have characterized PFC as a principal region exerting control over ventral striatum during CER, with the effect being related to individual differences in reappraisal ability (Kober et al., 2010; Wager, Davidson, Hughes, Lindquist, &

Ochsner, 2008). Furthermore, based on previous studies, aPE-related activity in the ventral striatum was enhanced during specific emotional states such as CER (Mulej Bratec et al., 2015) or stress (Robinson et al., 2013). CER also affects interactions among brain regions, such that during CER, synchronicity of activity between prefrontal regions, involved in regulation, and subcortical regions, typically suppressed during CER, is increased, with the effect being related to participants' reported negative feelings (Banks, Eddy, Angstadt, Nathan, & Phan, 2007; Erk et al., 2010; Kohn et al., 2013). Critically, strong PFC activation, akin to that typically seen during CER implementation, was shown to reduce hippocampal and thalamic inputs into the ventral striatum in adult male rats, thus biasing the ventral striatal inputs in favour of cortical and against subcortical inputs (Calhoon & O'Donnell, 2013).

In light of the above-described background, the current study focused on the question of whether CER might affect the balance among competing ventral striatal afferents, and to what extent individual differences in reappraisal ability might play a role in this effect. We therefore measured the influence of remote brain regions on ventral striatal aPE activity, by way of combining model-based fMRI and psychophysiological interaction analysis (PPI) during aversive classical conditioning with and without CER. We hypothesized that a successful CER implementation by superior regulators would shift the balance of ventral striatal inputs in favour of PFC as opposed to subcortical ventral striatal afferents, while opposite might be true for inferior regulators.

Results

CER affects the influence of afferents on ventral striatal aPE signals

Motivated by the hypothesis that CER would impact the interaction between ventral striatal afferents and ventral striatum, we carried out four ANOVAs, based on four generalized PPI analyses, one for each ventral striatal afferent (i.e., PFC, hippocampus, amygdala and VTA) (Fig. 2A). PPI analysis measures how strongly an (afferent) region's activity contribution (physiological factor) to the ventral striatal aPE activity depends on CER (psychological factor Regulation Strategy with levels CER and NoCER) (Friston et al., 1997). We first examined the main effect of Regulation Strategy for the four ANOVAs: there was a significant influence decrease

during CER compared to NoCER for the PFC (F = 13.199, p = 0.002), amygdala (F = 7.825, p = 0.012) and VTA (F = 8.97, p = 0.008) on aPE-related activity in the ventral striatum, and a trend towards a significant decrease of hippocampus influence (F = 3.094, p = 0.096) (Fig. 2B, first row). Results demonstrate that in humans, the influence of striatal afferents on ventral striatal aPE signals is modulated by CER, in line with suggestions from animal models of emotional behaviour outlined in Fig. 1.

Reappraisal Ability Impacts the Way CER Affects the Competing Influences of Ventral Striatal afferents on aPE signals

We next examined whether CER success (i.e., reappraisal ability) was relevant for the way CER affected the competing influence of ventral striatal afferents on ventral striatal aPE signals. To create the factor Reappraisal Ability, participants were divided into two equal groups, based on their reappraisal ability score (i.e., difference in the emotional intensity ratings between CER and NoCER conditions). Average reappraisal ability equalled 0.99 (SD = 0.41); superior regulators (N = 10) had a mean reappraisal ability score of 1.31 (SD = 0.24, N = 10) and inferior regulators (N = 10) a mean reappraisal ability score of 0.67 (SD = 0.26, N = 10).

To see whether differences in reappraisal ability influenced the way ventral striatal afferents affected ventral striatal aPE activity during CER, we examined the interaction between Regulation Strategy and Reappraisal Ability for the four ANOVAs (Fig. 2B, second row). A significant interaction was revealed by the ANOVA focusing on the PFC influence (F = 8.264, p = 0.01), with planned t-tests revealing that Superior regulators showed no change in the PFC contribution to striatal aPE activity between CER and NoCER conditions (t = -0.591, p = 0.285), while Inferior regulators showed a decrease in the PFC impact on ventral striatal aPE signals during CER compared to NoCER conditions (t = -4.24, p = 0.001). ANOVAs focusing on hippocampus, amygdala and VTA influences on ventral striatum did not reveal significant interaction effects (hippocampus: F = 1.551, p = 0.229; amygdala: F = 1.219, p = 0.284; VTA: F = 1.575, p = 0.226).

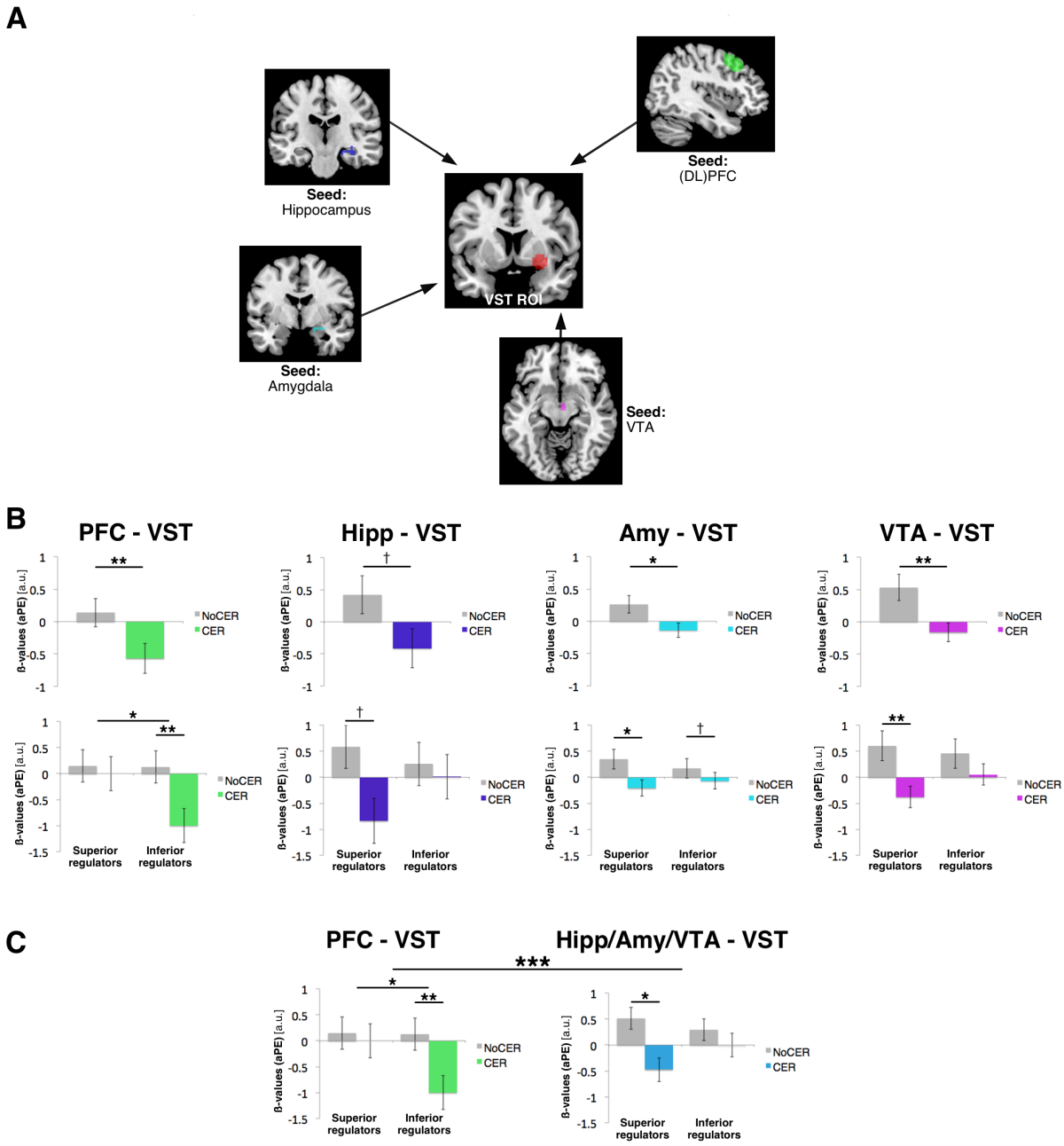

Figure 2. CER modulates the influence of ventral striatal (VST) afferents on striatal aPE signals. ***A,*** Overview of the PPI Analyses, including the four PPI seeds (PFC, hippocampus, amygdala and VTA), and the target ventral striatum ROI. ***B,*** First row shows the main effect of Regulation Strategy for each of the four PPI analyses; CER reduced the influence of ventral striatal afferents on ventral striatal aPE signals. Second row shows the Regulation Strategy × Reappraisal Ability interaction for each of the four connectivity combinations; the effect of CER on the influence of striatal afferents depended on individuals' reappraisal ability. **C,** The significant 3-way interaction shows that the impact of CER on the influence of striatal afferents on ventral striatal aPE signals was dependent on both the Ventral Striatal Afferent (PFC vs. Other Afferents) and Reappraisal Ability (Superior vs. Inferior regulators). Error bars indicate SEM. A.u. – arbitrary units, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, † trend ($p < 0.1$), n.s. – not significant.

We nevertheless examined planned t-tests for Superior and Inferior regulators, following the initial hypothesis regarding the impact of individual differences in reappraisal ability on ventral striatal influences during CER (Fig. 2B, second row). Planned t-tests revealed a significant decrease or a trend of hippocampus, amygdala, and VTA contribution to striatal aPE-activity during CER compared to NoCER for Superior regulators (hippocampus: t = -1.681, p = 0.064; amygdala: t = -2.292, p = 0.024; VTA: t = -3.505, p = 0.004), but no change (or a trend) for Inferior regulators (hippocampus: t = -0.572, p = 0.291; amygdala: t = -1.613, p = 0.071; VTA: t = -1.094, p = 0.151). Results suggest, in line with our hypothesis, that CER success or reappraisal ability is indeed relevant for the balanced influence of ventral striatal afferents on ventral striatal aPE signals, with a relatively higher impact of the PFC on ventral striatum during successful regulation.

Factor Ventral Striatal Afferent Additionally Impacts the Interaction Between Reappraisal Ability and Regulation Strategy

To directly investigate potentially distinct effects of CER success on the interaction between ventral striatal afferents and ventral striatal aPE signals, we further examined the interaction patterns between Regulation Strategy and Reappraisal Ability (Fig. 2B, second row), but now focusing on differences across ventral striatal afferents. Single region findings suggest that the Regulation Strategy × Reappraisal Ability interaction pattern for the PFC influence on ventral striatal aPE signals might differ from the patterns of hippocampus, amygdala, and VTA. To test this, we first carried out a 4 × 2 × 2 ANOVA with factors Ventral Striatal Afferent (PFC, hippocampus, amygdala, VTA), Reappraisal Ability (Superior, Inferior) and Regulation Strategy (NoCER, CER). Besides a main effect of Regulation Strategy (F = 10.439, p = 0.005), the ANOVA revealed a significant interaction between all three factors (F = 4.195, p = 0.01), representing a significant difference in Reappraisal Ability × Regulation Strategy interaction patterns between the four ventral striatal afferents. Then, to directly test the difference between PFC and the three subcortical afferents, we collapsed the results of hippocampus-, amygdala-, and VTA-focused connectivity analyses and compared the resulting interaction effect with the PFC-focused interaction pattern in a 2 × 2 × 2 ANOVA, with factors Ventral Striatal Afferent (PFC, Other Afferents), Reappraisal Ability (Superior, Inferior) and

Regulation Strategy (NoCER, CER). The ANOVA revealed a significant interaction between the three factors (F = 20.674, p = 0.0003), highlighting a significant difference in Reappraisal Ability × Regulation Strategy interaction patterns between the PFC and the three subcortical ventral striatal afferents (Fig. 2C). This significant 3-way interaction highlighted that the effect of CER on the balance between PFC and subcortical ventral striatal afferents' impact on ventral striatal aPE signals was significantly different for superior and inferior regulators (see schematic summary in Fig. 3).

Discussion

The current study investigated whether and how CER, a unique human ability to face emotional stimuli in a flexible way, modulates competing influences from distinct ventral striatal afferents on striatal aPE signals, critical for aversive conditioning. By investigating the contribution of ventral striatal afferents on ventral striatal aPE signals with and without CER, the study shows, for the first time, that CER can affect the balance among ventral striatal afferents, depending on the person's reappraisal ability (Figs. 2). Specifically, superior regulators shifted the balance in favour of PFC as opposed to subcortical ventral striatal afferents during CER, by reducing the contribution of subcortical ventral striatal afferents (hippocampus, amygdala and VTA) to ventral striatal aPE signals, while keeping the PFC contribution unchanged. Inferior regulators, on the other hand, showed an opposite pattern, with a decreased PFC influence and an unchanged contribution of subcortical ventral striatal afferents on ventral striatal aPE signals, highlighting the relevance of individual differences in reappraisal ability for the regulation of ventral striatal inputs (Figs. 2 & 3).

Current results demonstrate that CER affected the balanced influence of ventral striatal afferents on ventral striatal aPE signals in the network of motivated behaviour presented in Fig. 1. Specifically, all four ventral striatal afferents (i.e., PFC, hippocampus, amygdala, VTA) decreased their influence on striatal aPE activity during CER (Fig. 2B, first row). A previous animal study using in vivo intracellular recordings in adult male rats showed that burst-like activity from the medial PFC, akin to that typically seen during decision-making, induced a suppression of

hippocampal and thalamic inputs into the ventral striatum (Calhoon & O'Donnell, 2013). This is consistent with our finding that CER, requiring activity in the PFC and analogous to decision-making, reduced the strength of influence on the ventral striatum by its subcortical afferents: hippocampus, amygdala and VTA.

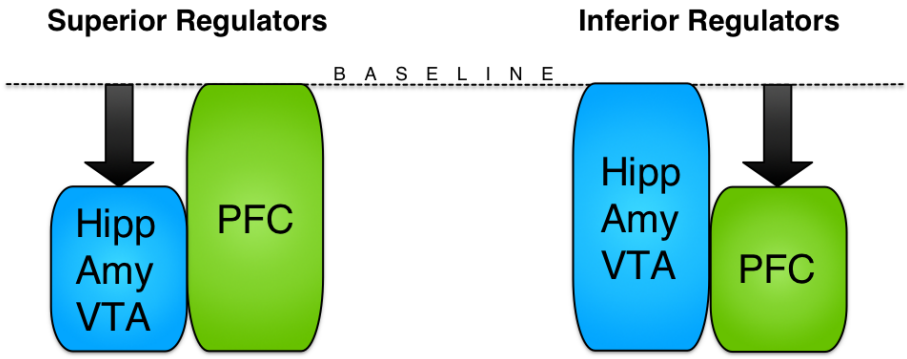

Figure 3. A schematic model summary of findings. As represented by the figure, superior regulators shifted the balance of VST inputs against the 'emotional and contextual' influences from the subcortical regions and in favour of the 'flexible' PFC influence, while inferior regulators exhibited an opposite balance shift.

Results of the study by Calhoon and O'Donnell, however, additionally indicate that a decrease of PFC influence might be counterproductive. Accounting for individual differences in reappraisal ability, we indeed observed a significant interaction between reappraisal ability and regulation strategy for the PFC influence on striatal aPE activity, such that superior regulators in fact preserved the contribution of PFC to ventral striatal activity during CER, while inferior regulators failed to do so (Fig. 2B, second row). Furthermore, superior regulators suppressed hippocampus, amygdala, and VTA contribution to ventral striatal aPE signals, while inferior regulators did not (Fig. 2B, second row). These differences between superior and inferior regulators, as well as cortical and subcortical ventral striatal inputs, were further confirmed in a significant 3-way interaction, showing that the impact of CER on the contribution of ventral striatal afferents to ventral striatal aPE signals was dependent on both the ventral striatal afferent (PFC vs. other afferents) and reappraisal ability (superior vs. inferior regulators) (Fig. 2C). In summary, superior regulators followed the expected pattern of preserving the influence of PFC and suppressing influences of subcortical ventral striatal afferents on the ventral

striatum (Calhoon & O'Donnell, 2013), thus shifting the balance of ventral striatal impact in favour of PFC and against subcortical ventral striatal inputs. Inferior regulators, on the other hand, exhibited the opposite pattern, reducing the influence of PFC on ventral striatal aPE signals and thus not being able to significantly reduce the influences on ventral striatum from subcortical ventral striatal afferents (Fig. 3).

According to contemporary view, the blood-oxygenation-level dependent (BOLD) response largely reflects local signal processing due to synaptic inputs rather than intrinsic neuronal firing within the region (Floresco, 2015; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). We therefore additionally examined the change of aPE-related *activation* in the ventral striatum ROI during CER in a supplementary analysis (see Supplementary Analysis and Supplementary Fig. S1). An increase of aPE-related activity during CER compared to NoCER conditions for Superior Regulators further confirmed the interpretation that a successful implementation of CER shifted the balance of ventral striatal inputs in favour of PFC and against subcortical inputs. The increase of aPE-related ventral striatal activity during CER might reflect a relative increase of the PFC input to the region and a relative decrease of subcortical inputs into the ventral striatum. We found no difference in aPE-related ventral striatal activation during CER compared to NoCER conditions for Inferior Regulators, confirming the lack of successful CER implementation in relation to ventral striatal input regulation (Supplementary Fig. S1).

The current findings could have significant implications for psychiatric disorders, particularly affective disorders characterised by impaired CER. The pattern of results for inferior regulators might provide an explanation for the behaviour of patients suffering from drug addiction or major depression. Such patients typically exhibit problems with emotion regulation, are less flexible in their behaviour and seem to be driven by the emotional and contextual information in the current setting, rather than long-term goals (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Cheetham, Allen, Yücel, & Lubman, 2010; Sheppes, Suri, & Gross, 2015). These problems might be driven by the inability to effectively shift the balance among

ventral striatal inputs in favour of the 'flexible' PFC and against the 'emotional and contextual' inputs from the subcortical regions.

Altogether, the current study provides new evidence that CER is able to affect the balance among competing ventral striatal inputs on ventral striatal aPE signals. Data suggest that a person with high reappraisal ability is able to relatively increase the PFC input into the ventral striatum and reduce the impact of subcortical ventral striatal afferents, such as hippocampus, amygdala, and VTA, on ventral striatal aPE signals.

Materials and Methods

Participants

Twenty-four healthy subjects (all female, mean age = 24.8 years, SD = 2.3 years) participated in the experiment, all native German speakers, right-handed, with normal or corrected-to-normal vision, and no history of neurological or psychiatric disorders, or intake of psychotropic medication. Two were excluded from further analysis due to excessive head movement (translation > 2 mm, rotation > 2°), and another two due to inadequate performance in the learning task. Owing to previous reports of gender differences regarding emotion processing and regulation, only female subjects were tested (McRae, Ochsner, Mauss, Gabrieli, & Gross, 2008; Nolen-Hoeksema, 2012; Whittle, Yücel, Yap, & Allen, 2011). The study was approved by a local ethics committee (Technische Universitaet Muenchen) and written informed consent was obtained from all participants. All methods were carried out in accordance with relevant guidelines and regulations and all experimental protocols were approved by the in-house Review Board of the Department of Medicine at the Technische Universitaet Muenchen.

Experimental Design and Tasks

During a conditioning paradigm with varying CS-US contingencies (Gläscher & Büchel, 2005; Mulej Bratec et al., 2015), a trial started with a fixation cross (1 s), after which the Regulation Instruction ('Distance' for CER and 'Attend' for NoCER) was presented (2 s). Then, a CS (blue square or yellow pentagon) was shown (6 s). Participants indicated whether a negative picture or no picture would follow the CS

via a button press in the first 3 s of CS presentation. The US (6 s) was a negative picture from the International Affective Picture System (Lang, Bradley, & Cuthbert, 1997), shown on 50% of the trials (Paired trials). The picture set was balanced for arousal and valence across CER and NoCER conditions. Next, participants had 3 s to indicate their emotional state via a button press on a scale from -3 to 3 (increments of 1; set to 0 on each trial). The inter-trial interval lasted for 4 ± 2 s. Each participant completed both CER (i.e., self-distancing) and NoCER (i.e., attentively observing) runs, with the run order counterbalanced across subjects.

The CS-US contingency fluctuated throughout each run (low-frequency sine-wave function, with 1.75 and 1.5 cycles for CS1 and CS2, respectively). The phase between the two sine functions was shifted by 96° so that each CS predicted US occurrence with a different probability at each time point (Gläscher & Büchel, 2005; Mulej Bratec et al., 2015). Participants were told that the two symbols (whose assignment to a particular CS-US contingency was counterbalanced across participants) predicted US occurence with different probabilities, and that they should keep in mind that these probabilities could change.

There were two experimental runs (CER and NoCER) of 80 trials each, with an equal proportion (40 trials) of CS1 and CS2 trials. A pseudorandom CS event train was used and the same CS could occur on no more than two consecutive trials. An average reinforcement probability of 50% resulted in 40 Paired and 40 non-Paired trials in each run. CS1 and CS2 were followed by an equal number of Paired trials (i.e., 20) in each run. The sine waves were used as threshold functions for the trial sequence. A trial was Paired or non-Paired when a random number drawn from the amplitude range was below or above the threshold function, respectively.

For the learning task, participants were asked to predict the occurrence of a US after a particular CS. In the CER condition of the regulation task, participants actively down-regulated emotions elicited by the negative pictures by means of reappraisal or cognitive self-distancing (Kalisch et al., 2005; Ochsner et al., 2004; Walter et al., 2009). As trained before the experiment, they took a stance of a detached third person, reminding themselves that the images were not real or were not related to

them or their loved ones. In the NoCER condition, participants let the images passively sink in without changing the evoked emotions. All participants complied with experimental instructions regarding the tasks.

Reappraisal Ability

Participants rated their emotional feeling at the end of each trial, for a behavioural measure of reappraisal ability. Only Paired trials were considered, since participants typically use CER chiefly when presented with negative pictures (Mulej Bratec et al., 2015). Regulation success was calculated as a difference in rating scores between CER and NoCER conditions. To account for individual differences in reappraisal ability (McRae, Jacobs, Ray, John, & Gross, 2012), participants were divided into two groups of equal size, resulting in 'superior' (regulation success > 1) and 'inferior' (regulation success < 1) regulators.

Computational Model

APEs were computed based on the Rescorla Wagner (RW) rule (Rescorla & Wagner, 1972). For a trial *t*, aPE was calculated as a difference between the actual outcome *R(t)* and the predicted outcome *aP(t)*:

$$aPE(t) = R(T) - aP(t) \times U(t)$$

In turn, predicted outcome for the next trial $aP(t+1)$, was updated by adding aPE of the current trial *aPE(t)* to *aP(t)*, weighted by a learning rate λ:

$$aP(t+1) = aP(t) + \lambda aPE(t) \times U(t+1)$$

We used a low λ of 0.05, based on previous studies (Gläscher & Büchel, 2005; Ouden, Friston, Daw, McIntosh, & Stephan, 2009). For more details on the model see Supplementary Methods.

MRI Acquisition

Measurements were performed on a 3T Siemens scanner at the Klinikum rechts der Isar, Technische Universitaet Muenchen, following a standard protocol. For more details, see Supplementary Methods.

fMRI Data Analysis

Analyses were carried out with SPM8 (Wellcome Department of Cognitive Neurology, London, UK). The T2*-weighted functional images were slice-timed, then realigned to the first image of the first run (after discarding the first two volumes) and unwarped. T1-weighted structural images were coregistered to the functional images, segmented and then normalized to a standard T1 template in the Montreal Neurological Institute (MNI) space with a 1 × 1 × 1 mm resolution. Normalization parameters from the latter were used to normalize the functional images, which were then resampled to 3 × 3 × 3 mm, smoothed with an 8 mm full-width-at-half-maximum Gaussian filter, and temporally high-pass filtered with a cut-off of 128 s.

General linear model (GLM)-based statistical analysis with the following regressors was performed: hemodynamic response function (HRF)-convolved a) onsets of CS1, CS2, US-Paired, US-nonPaired, Regulation Instructions, and Valence Scale; b) aP and aPE values derived from the RW rule as parametric modulations (PM) of the onset regressors: aP1 and aP2 as PM of CS1 and CS2 onsets, respectively, plus aPE-Paired and aPE-nonPaired as PM of US-Paired and US-nonPaired onsets, respectively; and c) 6 movement regressors derived from realignment as regressors of no interest. Since distancing is chiefly utilized during US presentation (Mulej Bratec et al., 2015), analyses of the current study focused on Paired trials only.

To test whether CER affected the influence of ventral striatal afferents on ventral striatal aPE signals, a generalized PPI analysis was carried out (McLaren, Ries, Xu, & Johnson, 2012). PPI analysis allows one to examine whether a BOLD signal in one region can be explained by an interaction of a BOLD signal in another region (the physiological component) and an experimental factor (the psychological component) (Friston et al., 1997). In the current study, the physiological component was the BOLD signal in each ventral striatal afferent, the psychological component

was Regulation Strategy, and the target was aPE-related activity in the ventral striatum. Considering the two interpretations of any PPI effect (Friston et al., 1997), we followed the interpretation that CER would affect the extent of activity contribution from ventral striatal afferents to aPE-related activity in the ventral striatum.

Based on the model of motivated behaviour (Fig. 1) (Grace et al., 2007; Pennartz et al., 2011), ventral striatal afferents (i.e., PFC, hippocampus, amygdala and VTA) were used as PPI seeds, resulting in four PPI analyses (Fig. 2A). The target ROI for all PPI analyses was a right ventral striatum ROI, based on a recent study that investigated the effect of stress on aPE-related activity in the ventral striatum (Robinson et al., 2013). A spherical ROI with a centre at x = 26, y = 6, z = -8 and an 8 mm radius was used. Seed ROIs for the PPI analyses were defined by contrasts reported in a previous study (Mulej Bratec et al., 2015), additionally restricted by anatomical regions as specified by the model of motivated behaviour (Table 1). Anatomical masks were defined by the WFU PickAtlas in SPM8 [http://fmri.wfubmc.edu/software/pickatlas] for amygdala, hippocampus and PFC, and by a custom-made box with x = [0 6], y = [-13 -7], z = [-11 -5] for VTA. Due to the right-sided target in the ventral striatum, only right-hemisphere seeds were considered, for simplicity of analysis. For amygdala, hippocampus and VTA, time-courses for each region and each participant were extracted from the contrast aPE-Paired: CER > NoCER, due to our interest in both the influence on aPE signals in the ventral striatum and the CER-related changes in this influence (Mulej Bratec et al., 2015). The PFC seed, typically a regulatory region, was defined by the right DLPFC cluster involved in CER (from the contrast US-Paired: CER > NoCER) (Mulej Bratec et al., 2015). Average ß-values related to the PPI-aPE regressor were extracted from the ventral striatum ROI and four separate 2 × 2 flexible factorial ANOVAs were carried out in SPSS, with factors Regulation Strategy (CER, NoCER) and Reappraisal Ability (Superior, Inferior). Considering multiple comparisons due to four separate analyses, a connectivity result survived the Bonferroni correction if $p < 0.05/4$ or $p < 0.0125$.

Table 1. Summary of PPI Analyses Seeds.

PPI Seed	Peak voxel x, y, z	ROI size in voxels
PFC	39, 20, 52	191
Hippocampus	24, -22, -11	47
Amygdala	24, 2, -14	15
VTA	6, -10, -11	12

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Supplementary Information

Cognitive Emotion Regulation Modulates the Balance of Competing Influences on Ventral Striatal Aversive Prediction Error Signals

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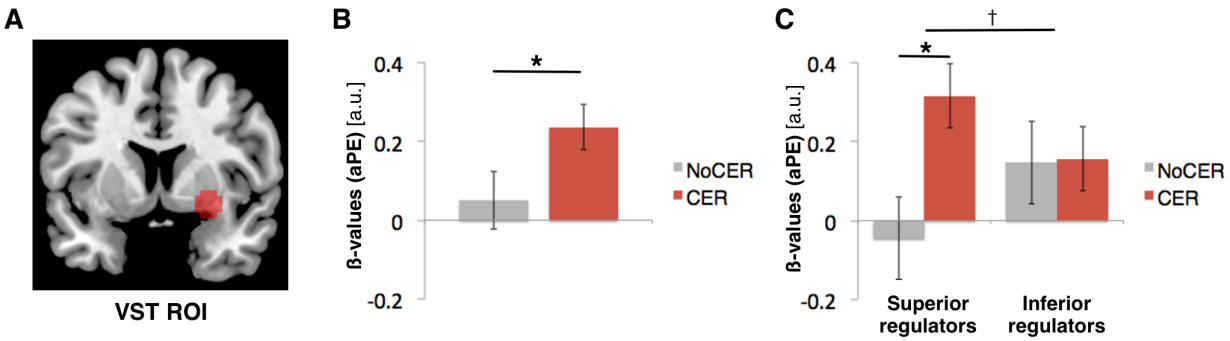

Supplementary Figure S1. CER-related enhancement of aPE-related VST activity and its dependence on reappraisal ability. ***A,*** VST ROI. ***B,*** CER enhanced aPE-related activity in the VST ROI, as shown by the significant main effect of Regulation Strategy. ***C,*** The enhancement of aPE-related activity with CER was related to individuals' reappraisal ability, as shown by a trend for a Regulation Strategy × Reappraisal Ability interaction. Superior regulators significantly increased the aPE-related VST activity during CER, while inferior regulators did not. Error bars indicate SEM. A.u. – arbitrary units, * $p < 0.05$, † trend ($p < 0.1$), n.s. – not significant.

Supplementary Methods

Computational Model

Aversive predictions (aPs) and aPEs were computed based on the Rescorla Wagner (RW) rule (Rescorla and Wagner, 1972). For a trial *t*, aPE was calculated as a difference between the actual outcome *R(t)* and the predicted outcome *aP(t)*:

$$aPE(t) = R(T) - aP(t) \times U(t)$$

In turn, predicted outcome for the next trial *aP*(*t+1),* was updated by adding aPE of the current trial *aPE(t)* to *aP(t)*, weighted by a learning rate λ:

$$aP(t+1) = aP(t) + \lambda aPE(t) \times U(t+1)$$

Parameter R was set to 1 when the aversive picture was delivered, and to 0 when no picture was shown. In turn, parameter *U* was used to disentangle CS1 and CS2 trials. Specifically, to calculate aP and aPE values related to CS1, *U* was set to 1 on CS1 trials, and to 0 on CS2 trials, and vice versa for the calculation of aPs and aPEs related to CS2 (Mulej Bratec et al., 2015).

We used a low λ of 0.05, based on previous studies {Glascher:2005cf, denOuden:2009gl}, firstly, due to the similarity of design, and secondly, because

they identified this specific learning rate to be relevant for VST, the primary target region in the current study. Furthermore, the same λ of 0.05 was also found to be relevant for amygdala and hippocampus {Glascher:2005cf, denOuden:2009gl} – emotion-relevant regions typically affected by CER and serving as VST afferents in the network of motivated behaviour (Figure 1) (Grace et al., 2007; Ochsner et al., 2012).

MRI Acquisition

Measurements were performed on a 3T Siemens scanner at the Klinikum rechts der Isar, Technische Universitaet Muenchen. Visual stimuli, presented with Presentation software (Neurobehavioral Systems), were rear-projected on a screen at scanner head and were visible via an adjustable mirror mounted to a standard head coil. Presentation software also received trigger pulses from the scanner.

Anatomical images were acquired with the magnetization-prepared rapid acquisition gradient echo (MP-RAGE) T1-weighted sequence (1 × 1 × 1 mm resolution), and functional scans with the contrast-gradient echo-planar T2*-weighted sequence with a repetition time of 2 s, echo time of 30 ms, flip angle of 90°, acquisition matrix of 64 × 64, 35 slices, each 3 mm thick, with a gap of 0.6 mm, and an in-plane resolution of 3 × 3 mm.

Supplementary Analysis

Effects of Regulation Strategy and Reappraisal Ability on aPE-related VST activation

Following the prediction that CER would also affect aPE-related activity in the VST, average ß-values related to the aPE regressor were extracted from the right VST ROI and a 2 × 2 flexible factorial ANOVA was carried out in SPSS, with factors Regulation Strategy (CER, NoCER) and Reappraisal Ability (Superior, Inferior). We first examined the Main effect of Regulation Strategy (i.e., CER vs. NoCER) and observed a significant enhancement of aPE-related activity in the VST ROI during CER (F = 4.475, p = 0.049) (Figure S1B). Next, to account for the effect of individual differences in reappraisal ability, we examined the interaction between Regulation Strategy and Reappraisal Ability. There was a trend towards a significant interaction (F = 3.984, p = 0.061), with planned t-tests revealing a significant

increase of VST aPE activity during the CER compared to the NoCER condition for Superior regulators (t = 2.486, p = 0.018), and no change in VST activity between NoCER and CER conditions for Inferior regulators (t = 0.106, p = 0.459) (Figure S1C). Results suggest that CER indeed affected aPE-related VST activity in superior regulators, but did not have an effect on VST activity in inferior regulators.

4

Project 3: How Do You Make Me Feel Better? Social Cognitive Emotion Regulation and the Default Mode Network

This chapter includes a research article entitled "How do you make me feel better? Social cognitive emotion regulation and the default mode network". The manuscript provides first insights into the neural correlates of social cognitive emotion regulation, and shows that the effectiveness of social emotion regulation is related to individual attachment security levels. The manuscript was published in NeuroImage in 2016.

Contributions:

Authors: *Xiyao Xie, Satja Mulej Bratec, Gabriele Schmid, Chun Meng, Anselm Doll, Afra Wohlschläger, Kathrin Finke, Hans Förstl, Claus Zimmer, Reinhard Pekrum, Leonhard Schilbach, Valentin Riedl, Christian Sorg*

The author of this thesis shares the first authorship of the manuscript with Xiyao Xie. X.X., **S.M.B.** and C.S. conceived the experiment, with the help of G.S., H.F. and C.Z. X.X. and **S.M.B.**, supervised by C.S., filmed G.S. to create social regulation videos used in the experiment. X.X. and **S.M.B.** together conducted behavioural and fMRI data acquisition, with the help of G.S. (the psychotherapist, as described in the manuscript). X.X. and **S.M.B.** analysed the behavioural and the neuroimaging data, with some help from C.M., A.D. and A.W., and under the supervision of V.R. and C.S. X.X. wrote the manuscript, which was revised by **S.M.B**. The writing was supervised by C.S., and the manuscript was commented on and additionally revised by K.F., R.P. and L.S.

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How do you make me feel better? Social cognitive emotion regulation and the default mode network

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ABSTRACT

Socially-induced cognitive emotion regulation (Social-Reg) is crucial for emotional well-being and social functioning; however, its brain mechanisms remain poorly understood. Given that both social cognition and cognitive emotion regulation engage key regions of the default-mode network (DMN), we hypothesized that Social-Reg would rely on the DMN, and that its effectiveness would be associated with social functioning. During functional MRI, negative emotions were elicited by pictures, and – via short instructions – a psychotherapist either down-regulated participants' emotions by employing reappraisal (Reg), or asked them to simply look at the pictures (Look). Adult Attachment Scale was used to measure social functioning. Contrasting Reg versus Look, aversive emotions were successfully reduced during Social-Reg, with increased activations in the prefrontal and parietal cortices, precuneus and the left temporo-parietal junction. These activations covered key nodes of the DMN and were associated with Social-Reg success. Furthermore, participants' attachment security was positively correlated with both Social-Reg success and orbitofrontal cortex involvement during Social-Reg. In addition, specificity of the neural correlates of Social-Reg was confirmed by comparisons with participants' DMN activity at rest and their brain activations during a typical emotional self-regulation task based on the same experimental paradigm without a psychotherapist. Our results provide first evidence for the specific involvement of the DMN in Social-Reg, and the association of Social-Reg with individual differences in attachment security. The findings suggest that DMN dysfunction, found in many neuropsychiatric disorders, may impair the ability to benefit from Social-Reg.

1. Introduction

From the very beginning of our lives, our emotions are influenced by others. Particularly, socially-induced emotion regulation from caregivers is the cornerstone for developing self-regulatory abilities (Calkins and Hill, 2007; Fox and Calkins, 2003), and interacts with the development of social functioning (Láng, 2010; Roque et al., 2013). In adulthood, emotions are often regulated by family members, friends, and – when emotions become a burden to our health – by professional therapists. Socially-induced cognitive emotion regulation (Social-Reg) is of particular interest. Cognitive emotion regulation (such as reappraisal, where one reinterprets the meaning of a stimulus in order to alter its emotional impact; Ochsner et al., 2012) is known to be one of the most effective ways of regulating emotions (Gross, 2014; Ochsner and Gross, 2005), and is widely applied both in everyday life (Niven et al., 2009) and in clinical practice (Cuijpers et al., 2013; DeRubeis et al., 2008). The current study focused on Social-Reg and its underlying brain mechanisms.

Abbreviations: Social-Reg, socially-induced cognitive emotion regulation; CBT, cognitive behavioral therapy; PFC, prefrontal cortex; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; TPJ, temporo-parietal junction; DMN, default mode network; Self-Reg, self-induced cognitive emotion regulation; OFC, orbitofrontal cortex; AAS, Adult Attachment Scale.

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1053-8119/

To accurately place the current study, we first clarify the relevant concepts linked with Social-Reg. In general, emotion regulation refers to a set of processes that can alter emotional experiences (Gross, 2014). Adding the social realm, emotions can either be regulated by the person experiencing them, termed *intrapersonal* emotion regulation (here referred to as self-induced emotion regulation), or by another person, termed *interpersonal* (Zaki and Williams, 2013) or social emotion regulation (Reeck et al., 2015) (here also referred to as socially-induced emotion regulation; the term 'induced' is used to explicitly stress the origin of regulation). Social emotion regulation and related phenomena have recently received increased attention across multiple research domains, particularly in social and cognitive neuroscience. For instance, verbal support from others, like emotional supportive messages and empathic paraphrasing, has been shown to attenuate negative feelings induced by socially unpleasant events (Onoda et al., 2009; Seehausen et al., 2012); likewise, holding hands or viewing photos of one's partner was also reported to reduce fear and fear-related neural activations induced by electric shocks (Coan et al., 2006; Eisenberger et al., 2011; Younger et al., 2010). Referring to these examples, we can further differentiate social emotion regulation from social emotion modulation. Social emotion regulation refers to a goal-driven process, in which one person (the regulator) regulates another person's (the target's) emotions (Reeck et al., 2015; Zaki and Williams, 2013), while social emotion modulation is a more passive process, which often occurs outside of any explicit goal (Zaki and Williams, 2013). In more detail, if people wish to influence their own emotions by engaging an external regulator, the process is referred to as *intrinsic* social emotion regulation (Gross, 2013, 2014, 2015; Zaki and Williams, 2013). For example, people draw on others' support as a resource to attenuate negative affect and intensify positive affect (Gable and Reis, 2010; Rimé, 2009). On the other hand, if the regulatory process is initiated by the regulator in order to target the emotions of another person, this is called *extrinsic* social emotion regulation (Gross, 2013, 2014, 2015; Zaki and Williams, 2013). It has been shown that people attempt to regulate others' emotions through empathic and supportive behaviors (Batson, 2011; Niven et al., 2009). Furthermore, a recent neuroimaging study found that the attempt to regulate another's emotions activated brain regions linked with both affective and cognitive empathy (Hallam et al., 2014).

Social-Reg is particularly important, both for general well-being and in psychotherapy. Social-Reg refers to the process during which the regulator provides the target with alternative interpretations for emotion-triggering stimuli in order to alter the target's emotions (Reeck et al., 2015). Besides their effectiveness, cognitive strategies for emotion regulation are highly adaptive, and are especially valuable when the stimulus has to be approached or is unavoidable (Gross, 1998; Ochsner et al., 2012). In daily life, when people are troubled with emotional difficulties, positively reframing the situation or talking about their opportunities can foster a positive outlook on the situation so as to help them overcome negative affect (Burleson, 2003; Clark et al., 1998). Importantly, Social-Reg is also a main treatment strategy for neuropsychiatric disorders featured with impaired emotion regulation (e.g., major depression and anxiety) (Borkovec and Ruscio, 2001; Cuijpers et al., 2013; DeRubeis et al., 2008; Frewen et al., 2008). In cognitive–behavioral therapy (CBT), for example, a therapist instructs and guides the patient to identify and change negative thoughts through a series of treatment sessions (Beck, 1997; Butler et al., 2006). Social-Reg in psychotherapy is an essential approach to equip patients with skills of identifying and regulating emotions — to ultimately train them to become their own therapists (Berking et al., 2013; Biesheuvel-Leliefeld et al., 2015; Neacsiu et al., 2014).

Despite its relevance in both daily life and the clinical context, the neural basis of Social-Reg remains poorly understood. The neural processes underlying Social-Reg in the target likely overlap with those of social cognition and cognitive emotion regulation (Reeck et al., 2015). Social cognition encompasses all processes dealing with social information, such as perceiving, thinking about, and making sense of ourselves and others in the social world. It relies on a distributed set of brain areas, such as the medial prefrontal cortex (PFC), anterior and posterior cingulate cortex (ACC and PCC, respectively), precuneus, and the temporo-parietal junction (TPJ) (for reviews, see Adolphs, 2009; Frith, 2007; Lieberman, 2007). Cognitive emotion regulation, on the other hand, refers to cognitive processes for managing emotional events and responses (e.g., reappraisal; Ochsner and Gross, 2005). Existing findings suggest that cognitive emotion regulation relies on the dorsolateral and dorsomedial PFC as well as parietal cortices (Buhle et al., 2014; Ochsner et al., 2012).

Interestingly, brain structures involved in social cognition and cognitive emotion regulation overlap in prefrontal and parietal lobes, more specifically, in areas of the so-called default mode network (DMN). The DMN is an intrinsic brain network of coherent ongoing low-frequency activity, initially identified during resting-state (i.e., a state of passive viewing or with eyes closed without performing a task) as a task-negative network (Amft et al., 2015; Andrews-Hanna, 2012; Buckner et al., 2008; Raichle et al., 2001). However, recent evidence revealed that the DMN is in fact consistently activated during tasks involving social, affective and introspective processes (Mason et al., 2007; Northoff et al., 2006; Schilbach et al., 2008). Even more, an explicit overlap has been reported between the resting-state DMN and areas related to social cognition in the dorsomedial PFC, precuneus and TPJ (Amft et al., 2015; Mars et al., 2012; Schilbach et al., 2012). Critically, aberrant functioning of the DMN is a prominent neurophysiological vulnerability for psychiatric disorders hallmarked by emotion dysregulation, such as major depression (Broyd et al., 2009; Hamani et al., 2011; Orosz et al., 2012).

Besides its neural basis, it also remains unexplored whether the effectiveness of Social-Reg or the DMN involvement during Social-Reg might interact with certain individual characteristics of social functioning, such as attachment security. Adult attachment security refers to the extent to which one is willing to trust and rely on others, which is an important modulator of social–emotional information processing (Mikulincer and Shaver, 2008; Vrtička and Vuilleumier, 2012). Existing studies found that the attachment security level shaped the effects of social support on pain ratings and associated neural processing (Hurter et al., 2014; Krahé et al., 2015; Sambo et al., 2010).

Considering the above-presented background, we inferred the following hypotheses. First of all, we expected that Social-Reg would recruit regions of the DMN due to their involvement in both social cognitive processes and cognitive emotion regulation. In addition, we expected that people would vary in the extent to which they benefit from Social-Reg based on their social functioning, as measured with the individual attachment security. Moreover, we also expected a positive association between attachment security and DMN involvement during Social-Reg.

To test these hypotheses, we conducted a functional MRI (fMRI) experiment, in which pictures were used to elicit aversive emotions in healthy individuals. A psychotherapist either down-regulated participants' emotions by employing the reappraisal strategy, or asked them to simply look at the pictures without changing their emotions. Contrasting these two conditions allowed us to identify the neural correlates of Social-Reg. To investigate the relationship of Social-Reg with social functioning, participants' attachment security was measured by the Adult Attachment Scale, and linked to both Social-Reg effectiveness and Social-Reg-related brain activations. To further specify the neural correlates of Social-Reg, two additional control experiments were included. 1) To formally assess the link between neural correlates of Social-Reg and the DMN, resting-state fMRI was carried out to identify the participants-specific DMN; we then compared Social-Reg-related activations with this DMN. 2) To examine whether Social-Reg was distinct from self-induced cognitive emotion regulation (Self-Reg), the same experimental procedure was repeated without a psychotherapist, wherein participants either actively down-regulated their emotions

using reappraisal or passively looked at the pictures. Neural correlates of Social-Reg were then compared with those of Self-Reg.

2. Materials and methods

2.1. Participants

After giving informed consent, twenty-two females (aged between 22 and 32 years, $M = 24.95$, $SD = 2.30$; all right-handed) participated in the study, which was approved by the local ethics committee (Technische Universität München). Only females were tested to prevent previously reported gender differences in emotion regulation (McRae et al., 2008). All participants reported no history of mental or neurological disorders, no current use of psychoactive medications, were native German speakers, and had normal or corrected-to-normal vision. 3 participants were excluded from the analysis due to excessive head movement (n = 2; cumulative translation or rotation >2 mm or 2°) or failure to comply with instructions (n = 1; negative Social-Reg success) during the fMRI experiment.

2.2. Experimental paradigm for Social-Reg

The experimental paradigm (Fig. 1) for Social-Reg was adapted from previous neuroimaging studies on cognitive reappraisal (Ochsner et al., 2004; Kim and Hamann, 2007; McRae et al., 2010; Mulej Bratec et al., 2015), such that an antecedent-focused strategy in the form of cognitive reappraisal was induced by a psychotherapist. Each trial began with a fixation cross presented for 1 s, followed by 1) an instruction phase (6 s), which varied between conditions to instruct participants on how to appraise the upcoming emotional stimulus; 2) an anticipation phase (6 s), during which participants waited for the emotional stimulus; 3) a picture presentation phase (6 s), to induce negative emotions; and 4) a rating phase (3 s), in which participants rated their emotional feelings (on a 7-point scale ranging from −3 = very negative to 3 = very positive). A black screen was presented for a jittered inter-trial interval (3 ± 2 s). During the picture presentation phase, aversive pictures from the International Affective Picture System (IAPS, Lang et al., 2005; the list of used pictures in the Supplementary methods) were presented to elicit negative emotions. Of main interest in the current study were picture-induced brain activations and their changes in different task conditions.

During the instruction phase, one and the same female psychotherapist instructed participants via a short video clip, in two conditions. In the regulation condition (Social-Reg), the psychotherapist regulated participants' emotions by helping them create mental distance from the negative pictures, using statements such as "*Don't forget, the pictures are not related to you*". The Social-Reg condition directly resembled socially-induced reappraisal (Reeck et al., 2015). Furthermore, all of the Social-Reg instructions were compiled based on a distancing strategy — a specific reappraisal strategy aiming to reduce emotional reactions through a detached perspective, e.g., suggesting that the emotional scenes are less personally relevant, are unreal, or are physically further away from observers (McRae et al., 2012). In the look condition (Social-Look), the psychotherapist told participants to look at the pictures and respond naturally, using statements such as "*Simply look at the picture*". Social-Look was an adapted version of the 'look' condition from previous neuroimaging studies on cognitive reappraisal (Ochsner et al., 2004; Kim and Hamann, 2007; McRae et al., 2010; Mulej Bratec et al., 2015). The order of the two conditions was counterbalanced across participants. The two conditions were carried out separately in two runs. Each run consisted of 80 trials (40 of which included a negative picture). Accordingly, 80 unique video clips of instructions were used for each condition (the list of instructions in the Supplementary methods). Participants were told that they should listen carefully to the instructions and follow them during the picture presentation. The psychotherapist thereby initiated and guided the regulatory process by providing an explicit reappraisal strategy for participants, conforming to the aforementioned definition of Social-Reg (Reeck et al., 2015). In respect of practice, the operation of deliberately providing instructions and guiding individuals to regulate their emotions is in line with the approach of Social-Reg used in psychotherapy (Berking et al., 2013; Biesheuvel-Leliefeld et al., 2015; DeRubeis et al., 2008; Jacobsen and Jim, 2008; Marroquín, 2011) and in daily life (Niven et al., 2009). Participants were also told to entrust the psychotherapist with the regulation procedure, to not judge the contents of the instructions, and to not use any other strategies on their own.

Critically, before the experiment, the psychotherapist was introduced face-to-face to the participant as an expert who would accompany and assist them via a communication system during the task by providing online instructions. Participants were informed that the psychotherapist was able to see them during scanning, and that they should follow her guidance. In this way, we attempted to build a comparatively real social context. This seemingly face-to-face communication is called para-social interaction in mass media research (Horton and Richard Wohl, 1956), which can provide a social milieu where the primary properties of a social interaction and sociability are demonstrated and reaffirmed (Giles, 2002; Perse and Rubin, 1989; Schiappa et al., 2007). It's noteworthy that the psychotherapist was introduced to the participants as an expert in emotion regulation to develop participants' trust in her and to ensure they would follow her instructions without doubt

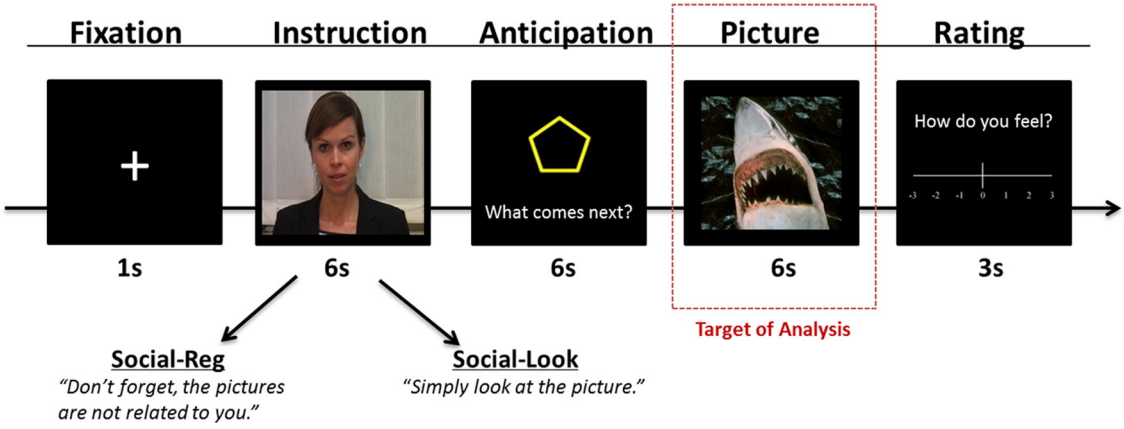

Fig. 1. Trial structure of the Social-Reg task. In the Social-Reg task, each trial consisted of a fixation cross, an instruction and anticipation phases, a negative picture, and a rating scale, with varying inter-trial intervals (3 ± 2 s). The instruction was a 6 s video clip, in which a psychotherapist regulated participants' emotions by using a distancing strategy, or told participants to look at and respond naturally to the pictures, depending on the condition. In the anticipation phase, participants were asked to predict whether a negative picture or no picture (i.e., a blank screen) would follow the presented cue. The analysis focused on brain activity during picture presentation, contrasting Social-Reg and Social-Look.

or hesitation. It was also emphasized to the participants that the psychotherapist's intention was to help them feel better and that they should cooperate with the psychotherapist to accomplish the task, through which a connection similar to the 'work alliance' in real-life psychotherapy was established between the participant and the psychotherapist during the experiment. Before the experiment, participants were trained with the same paradigm, but observed pre-recorded videos of a fellow female colleague instead of the psychotherapist, to prevent them from suspecting the reality of the "online" communication with the psychotherapist during scanning. They practiced until they were confident that they could understand and follow the instructions in the videos. For a more detailed description of the experimental procedure, see the Supplementary methods.

2.3. Experimental paradigm for control experiments

In order to specify the neural correlates of Social-Reg, two additional control experiments were included, which identified participants' DMN at rest and neural correlates of Self-Reg, respectively.

2.3.1. Resting-state assessment

To assess the extent to which the neural correlates of Social-Reg covered the DMN, an 8-min resting-state scan was conducted before the tasks to identify the group-specific DMN. Participants were instructed to keep their eyes closed, remain still, stay awake, and not think about anything in particular.

2.3.2. Self-Reg task

To specify the neural correlates of Social-Reg, the Social-Reg task was complemented with a standard Self-Reg task (Ochsner et al., 2004; Kim and Hamann, 2007; McRae et al., 2010; Mulej Bratec et al., 2015), based on the same paradigm and using the same participants (Fig. S1). In this task, the emotion regulation instructions were presented via a written word cue (2 s). In the regulation condition (Self-Reg; cue = "*Distance*"), participants were instructed to down-regulate their emotions by employing a pre-learned distancing strategy (e.g., reminding themselves that the pictures are not real and/or do not affect them). It was emphasized that participants should do their best to generate appropriate distancing sub-strategies at the presentation of each emotional picture during Self-Reg. Participants were also reminded that they should only use the distancing strategy (rather than, for example, closing their eyes or thinking about something positive) to down-regulate their emotions. In the look condition (Self-Look; cue = "*Attend*"), participants were told to respond naturally while looking at the pictures.

The Social- and Self-Reg tasks were conducted a week apart. And in each task, the Reg and Look conditions were carried out separately in two runs. The order of the tasks and conditions was counterbalanced across participants.

2.4. Questionnaire on social functioning

Before scanning, participants completed the German version of the Adult Attachment Scale (AAS, Close Relationship Version, Schmidt et al., 2004) with 15 items rated along a 5-point Likert scale ranging from "strongly disagree" to "strongly agree". AAS includes three subscales 'Close', 'Depend', and 'Anxiety'. The Close-subscale measures the extent to which one is comfortable with intimacy and emotional closeness (5 items; e.g., "I am comfortable developing close relationships with others"; $\alpha = 0.84$). The Depend-subscale measures the extent to which one trusts and relies on others (5 items; e.g., "I know that people will be there when I need them"; $\alpha = 0.85$). Finally, the Anxiety-subscale measures the extent to which one is worried about being rejected or abandoned (5 items; e.g., "I often worry that a person important to me will leave me"; $\alpha = 0.51$). In line with previous studies, the attachment security score was calculated by summing up the Close and Depend subscales scores and subtracting the Anxiety subscale score (Goldman and Anderson, 2007).

2.5. Acquisition of imaging data

MRI images were collected on a 3 T Siemens Verio scanner. For co-registration and normalization, high-resolution T1-weighted 3D images were acquired with the magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequence ($1 \times 1 \times 1$ mm^3 resolution). During resting-state and task measurements, T2*-weighted functional images were acquired with the Echo-Planar Imaging pulse sequence (TE = 30 ms, TR = 2000 ms, flip angle = 90°, acquisition matrix = 64×64, 35 slices, each 3 mm thick, with a gap of 0.6 mm, and an in-plane resolution of 3×3 mm).

2.6. Analysis of imaging data

2.6.1. Preprocessing

All imaging data analysis was carried out with SPM8 (www.fil.ion.ucl.ac.uk/spm/) unless otherwise stated. Preprocessing steps of task fMRI data included the removal of the first two volumes, slice-timing correction, head motion correction, spatial normalization and smoothing. In more detail, realignment of functional images to the first functional image of the first scanning session was performed by using the rigid body transformation. Alignment of functional and anatomical (T1) images was estimated via the SPM8 coregistration module. For normalization, the T1 image was segmented into gray and white matter as well as cerebrospinal fluid and transformed into the ICBM template (Montreal Neurological Institute or MNI system). The received normalization parameters were used to transform the functional images into the MNI space. Normalized functional images were finally smoothed with a Gaussian kernel (FWHM = 8 mm).

2.6.2. Analysis of brain activations during Social-Reg

For the first-level analysis of each participant, preprocessed task fMRI images were entered into a General Linear Model, to estimate blood oxygen level dependent (BOLD) signal changes for each experimental condition. Onsets of emotion induction (i.e., picture presentation phase) were entered as the regressor-of-interest, while regressors-of-no-interest were created by onsets of other stimuli (i.e., fixation cross, and instruction, anticipation and rating phases), as well as the 6 movement parameters (to remove artificial motion-related signal changes). All regressors were convolved with the hemodynamic response function. Intrinsic autocorrelations were accounted for by the first-order autoregressive process, and low-frequency drifts were removed via a high-pass filter (128 s).

Individual contrast images of the first-level analysis were fed into a second-level random-effects group analysis, using a flexible factorial model with factors subject, instruction (Reg/Look), and task (Social/Self). The contrast Social-Reg vs. Social-Look was the contrast-of-interest, while other contrasts (as defined below) were used for control analyses. All contrasts were analyzed at a cluster-wise threshold of $p < 0.05$, family-wise error (FWE)-corrected, based on a height threshold of $p < 0.001$.

2.6.3. Brain-behavior correlation analysis

To investigate the relationship between the increase of brain activity during Social-Reg and both Social-Reg success (here referred to as regulation success for the Social-Reg − Social-Look difference in emotional rating scores) and attachment security, we extracted and averaged β-values for each significant cluster in the contrast Social-Reg > Social-Look, and correlated these values with corresponding behavioral scores using Pearson's correlation with a significance level of $p < 0.05$, uncorrected. Because the PFC cluster of Social-Reg > Social-Look was large (cluster size $k = 1212$) and covered several PFC sub-regions of likely distinct functions, we divided it into three sub-

regions to improve analysis specificity, namely the dorsomedial PFC, dorsolateral PFC, and the orbitofrontal cortex (OFC) following the Automated Anatomical Labeling (AAL) templates (i.e., Frontal_Sup_Medial_L/R; Frontal_Sup/Mid_L/R; Frontal_Sup/Mid_Orb_L/R).

2.6.4. Specificity control: comparison with the DMN at rest

To assess the degree of overlap between the neural correlates of Social-Reg and the DMN at rest, canonical high model order independent component analysis (ICA) was conducted on the resting-state fMRI data, with a subsequent template-based selection of the DMN (for details, see Supplementary analyses and results). Finally, spatial overlap of the contrast Social-Reg > Social-Look with the identified DMN was assessed.

2.6.5. Specificity control: comparison with brain activations during Self-Reg

To identify the neural correlates of Social-Reg, in contrast to Self-Reg, we examined the commonalities and differences between the Social- and Self-Reg tasks. Regarding the common regions (i.e., brain areas with significantly increased activations for both Social- and Self-Reg), we applied a conjunction approach, in which we used the contrasts Social-Reg > Social-Look and Self-Reg > Self-Look as inclusive masks for each other. Regarding the distinct regions (i.e., brain areas more active during the Reg condition compared to the Look condition *and* more active during one task – Social-Reg or Self-Reg – than the other), we examined the interaction contrasts instruction (Reg/Look) × task (Social/Self), i.e., the contrasts $(\text{Reg} > \text{Look})_{\text{Social}} > (\text{Reg} > \text{Look})_{\text{Self}}$ and $(\text{Reg} > \text{Look})_{\text{Self}} > (\text{Reg} > \text{Look})_{\text{Social}}$, which defined specific activations for Social-Reg and Self-Reg, respectively. To further determine whether significant activations from the interactions were restricted to areas that engaged in the regulation, we tested the interaction contrasts in conjunction with the contrasts Social-Reg > Social-Look and Self-Reg > Self-Look, respectively. The Fisher method of combining p values was used, to identify voxels that randomly activated in both contrasts at $p < 0.001$ (Lazar et al., 2002). Finally, two additional control analyses were performed to confirm that the specificity of brain activations for Social-Reg were still tenable after we (1) controlled for a possible session order effect; and (2) removed any possible carry-over effects of events that preceded the regulation phase (i.e., instruction and anticipation phases) (for details, see Supplementary analyses and results).

3. Results

3.1. Manipulation check

Post-experimental interview verified that all participants believed that the psychotherapist was indeed present throughout the scanning in an adjacent observation room, and that they engaged in the task by following the psychotherapist's guidance.

3.2. Regulation success of Social-Reg

Emotional rating scores were significantly higher during Social-Reg than during Social-Look (paired t-test, $t_{18} = 8.55$, $p < 0.001$, $d = 1.44$), indicating that Social-Reg effectively reduced participants' negative feelings (Fig. S2).

3.3. Neural mechanisms of Social-Reg

To analyze the effect of Social-Reg, we examined the contrast Social-Reg > Social-Look, and found enhanced activations in bilateral dorsolateral and dorsomedial PFC, bilateral OFC, dorsal ACC, inferior parietal cortex and precuneus (Fig. 2A, Table 1). Activations largely overlapped with key regions of the DMN identified in previous studies (Andrews-Hanna, 2012; Buckner et al., 2008). To evaluate whether the observed activations were indeed linked to emotion regulation, we further tested whether regulation success co-varied with activation changes of Social-Reg (Fig. 2B). Analysis showed that activations in the left inferior parietal cortex (peak at [−48–61 46], $k = 449$) and the precuneus (peak at [−3–70 43], $k = 279$) positively correlated with regulation success ($r = 0.73$, $p < 0.001$, and $r = 0.44$, $p < 0.05$, respectively). Other clusters that were significantly activated during Social-Reg were not correlated with regulation success (see Table S1).

To identify regions whose activity decreased during Social-Reg, we examined the contrast Social-Look > Social-Reg and found reduced activations in the bilateral supramarginal, temporal and occipital cortices, and the left insula (Fig. S3), areas known to be modulated by cognitive emotion regulation (Kanske et al., 2010; McRae et al., 2010).

3.4. Correlations between attachment security and Social-Reg

The association of individual differences in attachment security with Social-Reg at both behavioral and brain levels was tested by means of Pearson's correlation analysis (Fig. 3). At the behavioral level, attachment security scores were indeed positively correlated with regulation success ($r = 0.42$, $p < 0.05$). At the brain level, averaged beta values of the bilateral OFC from the Social-Reg activation pattern ($k = 34$, $r = 0.44$, $p < 0.05$) were also positively associated with attachment security. Other clusters that were significantly activated during Social-Reg were not correlated with attachment security (see Table S1). To further test the specificity of the correlation between Social-Reg and attachment security, similar correlations analyses were conducted for Self-Reg. No significant correlations were observed between attachment security and either Self-Reg success or Self-Reg brain activations (Table S2). In addition, we found trends towards significant differences between Social-Reg- and Self-Reg-related correlations at both behavioral and brain levels (details in Supplementary analyses and results).

3.5. Specificity of neural mechanisms of Social-Reg

3.5.1. Overlap between the neural mechanisms of Social-Reg and the DMN at rest

To further assess the degree of overlap with the DMN, brain activations of Social-Reg were compared with the DMN at rest identified in the current sample. ICA of resting-state fMRI data identified 4 DMN sub-networks (one-sample t-test, $p < 0.05$, FWE corrected), which were merged to represent the DMN as a whole (Fig. S4). The DMN included dorsal and ventral medial PFC, PCC, precuneus, and parietal and posterior temporal areas including TPJ (Fig. 4A), in line with previous findings (Andrews-Hanna, 2012; Buckner et al., 2008). A conjunction between the DMN and the Social-Reg recruited areas showed a large overlap in the medial and bilateral lateral PFC, bilateral inferior parietal cortex, and precuneus, which quantitatively represents more than 60% of all the Social-Reg recruited voxels (Fig. 4B).

3.5.2. Common and different neural mechanisms of Social-Reg and Self-Reg

To investigate the specificity of Social-Reg, areas recruited by Social-Reg were compared with those recruited by Self-Reg. At the behavioral level, Self-Reg also proved effective at reducing participants' negative feelings (paired t-test, $t_{18} = 10.29$, $p < 0.001$, $d = 2.38$) (Fig. S2). At the brain level, it yielded enhanced activations in bilateral dorsolateral and dorsomedial PFC, and inferior parietal cortex (contrast Self-Reg > Self-Look; Figs. 5A and S5A, Table S3), and reduced activations in the bilateral insula, occipital cortices, the left thalamus and the periaqueductal gray (contrast Self-Look > Self-Reg; Fig. S5B).

To directly compare Social- and Self-Reg effectiveness at the behavioral level, a planned t-test was conducted, comparing Social-Reg success (Social-Reg–Social-Look) and Self-Reg success (Self-Reg–Self-Look). The t-test showed that Self-Reg led to a greater reduction of negative emotional rating scores than Social-Reg ($t_{18} = 2.47$, $p < 0.05$, $d = 1.16$) (Fig. S2). This was expected, given that our participants were healthy young females, adept at Self-Reg, and regularly using it in their daily lives. At the brain level, both conjunction and interaction

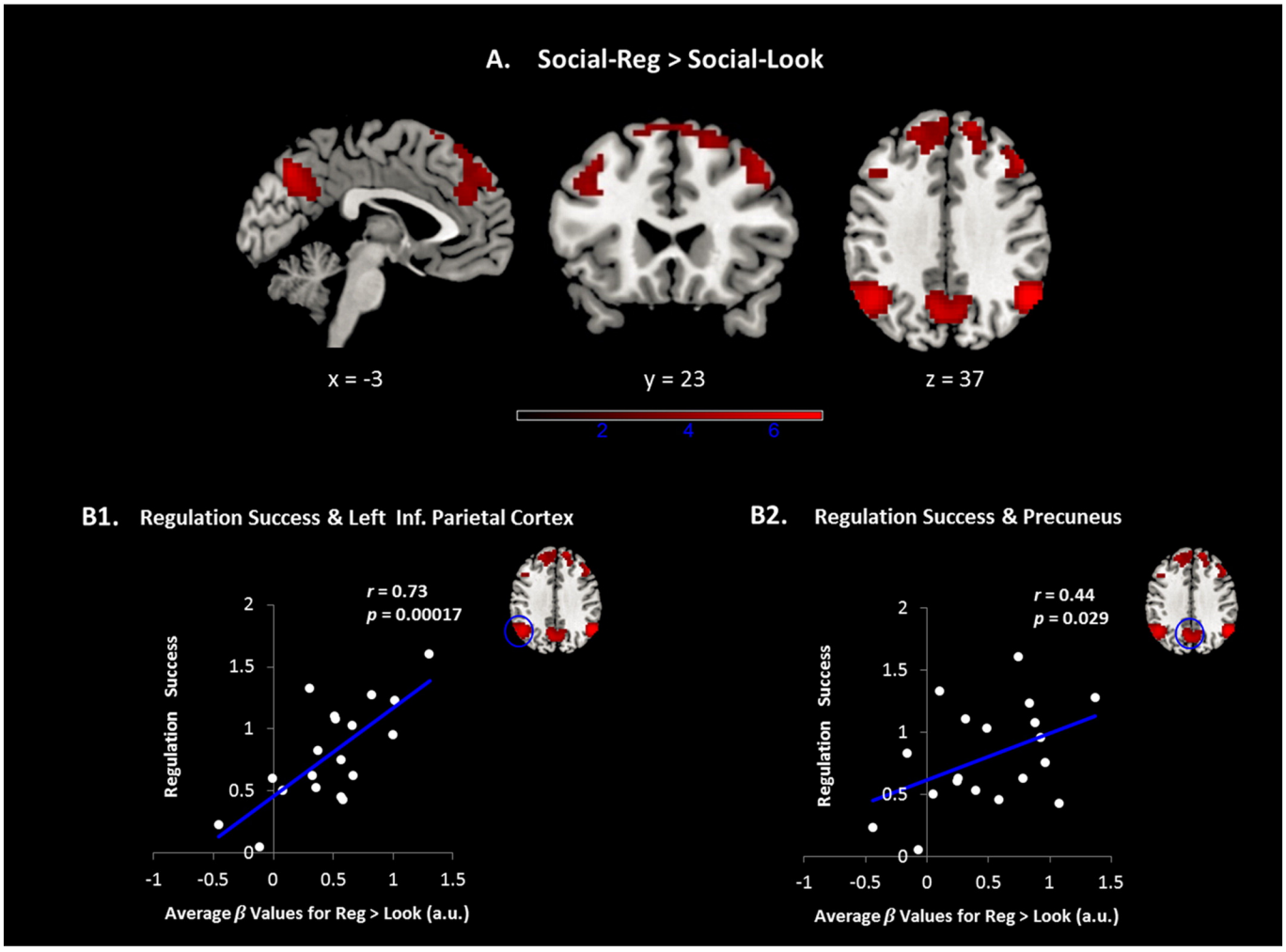

Fig. 2. Neural mechanisms of Social-Reg. (A) Brain areas recruited by Social-Reg were examined by the contrast Social-Reg > Social-Look ($p < 0.05$, FWE cluster-corrected). (B) During Social-Reg, brain activations in the left inferior parietal cluster (B1) (peak at [−48, −61, 46], $k = 449$), and precuneus cluster (B2) (peak at [−3, −70, 43], $k = 279$) positively correlated with Social-Reg success (Pearson's correlations, $p < 0.05$).

Table 1
Areas recruited by Social-Reg.

Brain region	H	BA	CS	MNI coordinates			T
				x	y	z	
Social-Reg > Social-Look							
Inferior parietal	R	39	231	51	−58	37	7.06
Inferior parietal	L	39	449	−48	−61	46	6.44
Superior frontal (DMPFC)	R	8/9/10	1212	18	56	25	6.00
Middle frontal (DLPFC)	R	9/44		45	29	40	5.63
Superior frontal (DMPFC)	L	9/32		−18	47	34	4.85
Superior medial frontal (DMPFC)	R	8		9	32	61	4.71
Middle orbital frontal (lateral OFC)	L	47		−36	53	−2	4.61
Superior medial frontal (DMPFC)	L	9/10		−3	53	43	4.35
Anterior cingulate		32		0	41	25	4.18
Superior orbital frontal (lateral OFC)	R	11		27	53	−2	3.99
Inferior frontal (DLPFC)	L	45		−36	44	13	3.88
Precuneus	L	7	279	−3	−70	43	5.67
Precuneus	R	7		9	−67	37	4.93
Posterior cingulate	L	23		−6	−52	28	3.46
Middle frontal (DLPFC)	L	9	84	−42	11	52	5.06
Inferior frontal (DLPFC)	L	44		−39	23	31	4.20

Note: Results are derived from a voxel-wise t-test based on the contrast Social-Reg > Social-Look. All results are shown at a cluster-wise threshold of $p < 0.05$, FWE corrected, based on a voxel-wise threshold of $p < 0.001$ and a minimum cluster size threshold of $k = 70$ voxels. Abbreviations: H, hemisphere; BA, Brodmann area; CS, cluster size in the number of activated voxels; L, left; R, right; DL, dorsolateral, DM, dorsomedial; OFC, orbitofrontal cortex; PFC, prefrontal cortex; and T, t-values for each given peak.

analyses were performed. Concerning commonalities, the conjunction between the contrasts Social-Reg > Social-Look and Self-Reg > Self-Look showed a significant overlap in the bilateral dorsolateral and medial PFC and the inferior parietal cortices (Fig. 5B, Table 2), as indicated by spatial overlaps in Fig. 5A. Concerning differences, distinct areas recruited by Social-Reg, i.e., areas with a stronger regulatory effect in the Social-Reg task, were tested by the interaction effect $(\text{Reg} > \text{Look})_{\text{Social}} > (\text{Reg} > \text{Look})_{\text{Self}}$ in conjunction with the effect of Social-Reg > Social-Look. This analysis yielded activations in the dorsomedial PFC, precuneus, and left TPJ (Fig. 5C, Table 3). Importantly, these regions partly overlapped with areas whose activation was positively related to the Social-Reg success (Fig. 2B), and remarkably overlapped with particular regions of the DMN that have been observed as critical for social cognition in a meta-analysis of imaging studies by Schilbach and colleagues (the 'social-DMN') (Schilbach et al., 2012) (Fig. 5D). In contrast, distinct areas preferentially involved in Self-Reg were tested by the conjunction between the contrasts $(\text{Reg} > \text{Look})_{\text{Self}} > (\text{Reg} > \text{Look})_{\text{Social}}$ and Self-Reg > Self-Look, which yielded the left triangular part of the inferior frontal gyrus, and the inferior parietal cortex (Table 3).

Finally, control analyses confirmed that the specificity of brain activations for Social-Reg was not confounded by either the session order effect (i.e., whether the Social-Reg or the Self-Reg task was conducted first) or potential carry-over effects of the instruction and anticipation phases (for details, see Supplementary analyses and results).

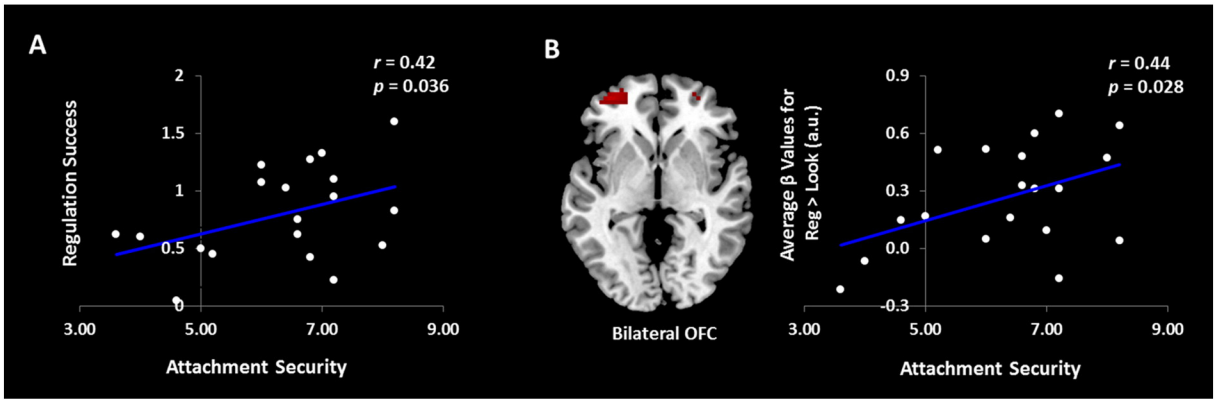

Fig. 3. Social-Reg correlation with attachment security at both behavioral and brain levels. (A) Behaviorally, Social-Reg success positively correlated with attachment security scores from the Adult Attachment Scale (AAS). (B) Regarding brain imaging data, activity changes in the bilateral OFC ($k = 34$) also positively correlated with attachment security scores (Pearson's correlations, $p < 0.05$). A.u.: arbitrary units.

4. Discussion

The present study used fMRI, aversive picture presentation, and socially-induced reappraisal in healthy females to investigate the brain mechanisms of Social-Reg. We found that (i) in contrast to Social-Look, Social-Reg reduced negative feelings and was related to increased activations in the dorsolateral and medial PFC and parietal cortices; (ii) individual differences in attachment security were positively associated with the degree of both Social-Reg success and lateral OFC involvement during Social-Reg. Specificity of the neural underpinnings of Social-Reg was confirmed by comparisons with both participants' DMN activity at rest and activations during Self-Reg. More specifically, Social-Reg recruited brain regions largely overlapped with the participants' DMN, and compared with Self-Reg, Social-Reg recruited specific activations in the left TPJ, dorsomedial PFC, and precuneus, which overlapped with the so-called 'social-DMN' as described in the meta-analysis by Schilbach et al. (2012). The findings provide first-time evidence that Social-Reg is subserved by the DMN and associated with individual differences in attachment security.

4.1. Neural mechanisms of Social-Reg

During Social-Reg, results showed significantly increased activations in a widely distributed medial and lateral prefrontal and orbitofrontal, as well as parietal–temporal network, in comparison with the Social-Look condition (Fig. 2A). Furthermore, activations in the parietal parts of this network were positively correlated with regulation success, indicating that the observed activations were relevant for down-regulating negative emotions during Social-Reg (Fig. 2B). To specify the nature of activations associated with Social-Reg in more detail, we directly compared the neural correlates of Social-Reg with those of Self-Reg. On the one hand, Social-Reg activations in the dorsolateral and medial PFC and the inferior parietal cortex overlapped with the activations related to Self-Reg (Fig. 5A, B). This prefrontal–parietal network is well known for its critical role in cognitive emotion regulation and top-down cognitive control (Buhle et al., 2014; Ochsner et al., 2012). The overlap, therefore, suggests that Social-Reg partly draws on resources from the general cognitive control network common to typical self-induced reappraisal. On the other hand, we found that beyond these regions, Social-Reg specifically recruited the left TPJ, dorsomedial PFC and precuneus (Fig. 5A, C). These brain regions are typically involved in complex social functions required for successful social interactions (Amodio and Frith, 2006; Carter and Huettel, 2013; Cavanna and Trimble, 2006). The specific recruitment of these brain regions indicates that Social-Reg also relies on social cognitive processes (e.g., comprehending the psychotherapist's intentions and actions, and shifting between one's own and the psychotherapist's perspective).

From an intrinsic brain network point-of-view, brain regions recruited by Social-Reg largely overlapped with the DMN (Fig. 4), which is generally critical for emotion processing and regulation (Lindquist et al., 2012; Sylvester et al., 2012). Previous findings have suggested that aberrant functioning of the DMN can result in emotional dysregulation (Broyd et al., 2009; Orosz et al., 2012; Schilbach et al., 2014; Sheline et al., 2009). Consistent with these findings, the DMN was engaged in Social-Reg in the present study. Remarkably, distinct activations of the Social-Reg partially overlapped with all three regions of the so-called 'social-DMN' (Fig. 5D), identified recently in a large-scale fMRI meta-analysis by overlapping DMN with brain regions typically involved in social cognitive processes (Schilbach et al., 2012).

The overlap between the Social-Reg activations and the DMN suggests a specific social–cognitive component in Social-Reg, mediated by the 'social-DMN'. Brain regions of the 'social-DMN' are consistently involved in tasks that require mental state attributions to oneself and others (Amodio and Frith, 2006; Keysers and Gazzola, 2007). Recently, the recruitment of these brain regions has also been shown during online social interactions as a function of the degree to which individuals connect and coordinate with each other (Fairhurst et al., 2013; Schilbach et al., 2010). Our findings support this view, as participants also reported to have experienced the communication with the

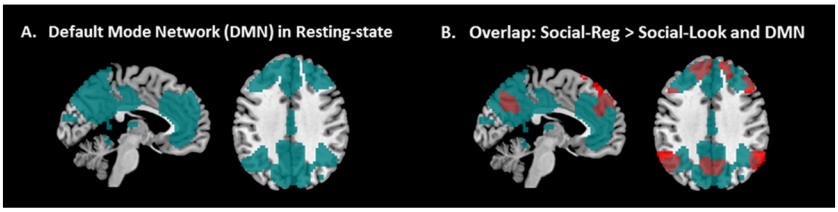

Fig. 4. Overlap of neural mechanisms of Social-Reg with the DMN. (A) The DMN was identified by group independent component analysis of resting-state fMRI data from the current participants (one-sample t-test, $p < 0.05$, FWE corrected). Analysis revealed four DMN sub-networks, which were then merged together. (B) Brain areas recruited by Social-Reg largely overlapped with the DMN.

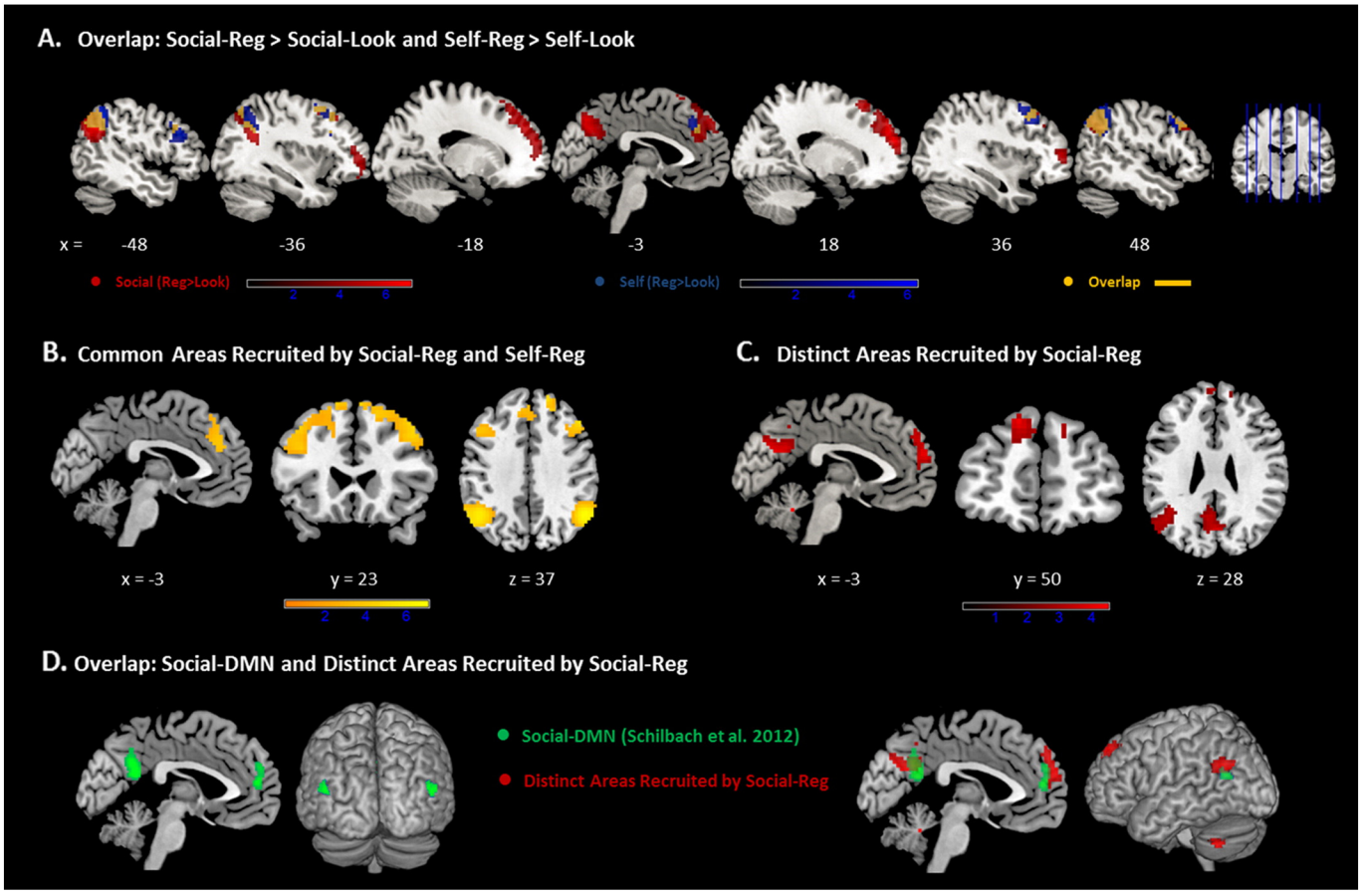

Fig. 5. Common and distinct neural mechanisms of Social-Reg and Self-Reg. (A) Overlapping areas (in yellow) recruited by Social-Reg (contrast Social-Reg > Social-Look, in red) and Self-Reg (contrast Self-Reg > Self-Look, in blue) ($p < 0.05$, FWE cluster-corrected). (B) Common areas recruited by both Social-Reg and Self-Reg, as examined with the conjunction analysis of the contrasts Social-Reg > Social-Look and Self-Reg > Self-Look ($p < 0.05$, FWE cluster-corrected). (C) Distinct areas recruited by Social-Reg, as examined by the conjunction analysis of the contrasts $(\text{Reg} > \text{Look})_{\text{Social}} > (\text{Reg} > \text{Look})_{\text{self}}$ and Social-Reg > Social-Look (height threshold $p < 0.001$, with a cluster extent of 15 voxels). (D) Overlap between the distinct areas recruited by Social-Reg and the 'social-DMN'. In the left panel, the 'social-DMN' boundary was identified by a previous ALE meta-analysis of social and unconstrained cognition (reproduced, with permission, from Schilbach et al., 2012). Right panel shows the overlap between the distinct areas recruited by Social-Reg and all three 'social-DMN' regions (i.e., precuneus, dorsomedial PFC and left TPJ).

psychotherapist as occurring in real-time in our post-experimental interview. Furthermore, precuneus and inferior parietal cortex, whose activations were directly linked to regulation success (Fig. 2B), belonged to areas specifically recruited by Social-Reg (Fig. 5C), suggesting a link between Social-Reg effectiveness and interaction with others.

In summary, our data suggest a dual-source model of Social-Reg, with a fronto-parietal source, common to typical Self-Reg, for top-

Table 2
Common areas recruited by Social-Reg and Self-Reg.

Brain region	H	BA	CS	MNI coordinates			T
				x	y	z	
$(\text{Reg} > \text{Look})_{\text{Social}} \cap (\text{Reg} > \text{Look})_{\text{Self}}$							
Inferior parietal	R	39	317	51	−58	37	7.06
Superior frontal (DLPFC)	R	9/10	628	18	56	22	5.16
Middle frontal (DLPFC)	R	9/44/47		21	50	28	5.79
Superior medial frontal (DMPFC)	R	8		9	32	61	4.71
Superior medial frontal (DMPFC)	L	32		−9	41	34	3.86
Angular	L	39	314	−48	−61	46	6.44
Middle frontal (DLPFC)	L	9/46	307	−42	11	52	5.06
Inferior frontal (DLPFC)	L	44		−39	23	31	4.20

Note: Results are derived from a conjunction approach by employing the respective contrasts as inclusive masks, at an overall cluster-wise threshold of $p < 0.05$, FWE-corrected, based on a voxel-wise threshold of $p < 0.01$ for each contrast, and a minimum cluster size threshold of $k = 266$ voxels. Abbreviations: H, hemisphere; BA, Brodmann area; CS, cluster size in the number of activated voxels; L, left; R, right; DL, dorsolateral, DM, dorsomedial; PFC, prefrontal cortex; and T, t-values for each given peak.

Table 3
Distinct areas recruited by either Social-Reg or Self-Reg.

Brain region	H	BA	CS	MNI coordinates			T
				x	y	z	
Distinct areas recruited by Social-Reg: $(\text{Reg} > \text{Look})_{\text{Social}} > (\text{Reg} > \text{Look})_{\text{Self}} \cap (\text{Reg} > \text{Look})_{\text{social}}$							
Cerebellum	L		15	−6	−55	−26	4.46
Lingual	L	18	146	−6	−64	2	3.99
Cuneus	R			3	−73	31	3.82
Precuneus	L			−6	−55	40	2.76
Angular (TPJ)	L	39	136	−39	−52	25	3.64
Superior frontal (DMPFC)	L	9/32	222	−12	50	43	3.61
Superior medial frontal (DMPFC)	L	10		−3	59	22	3.60
Superior frontal (DMPFC)	R	9/10		18	56	25	2.84
Superior medial frontal (DMPFC)	R	10		9	59	19	2.70
Distinct areas recruited by Self-Reg: $(\text{Reg} > \text{Look})_{\text{Self}} > (\text{Reg} > \text{Look})_{\text{social}} \cap (\text{Reg} > \text{Look})_{\text{Self}}$							
Inferior frontal (IFG)	L	48	27	−42	26	25	3.35
Inferior parietal	L	40	41	−42	−46	49	3.11

Note: Results are derived from a conjunction approach by employing the interaction effects and respective contrasts as inclusive masks, at an overall voxel-wise threshold of $p < 0.001$ (a voxel-wise threshold of $p < 0.01$ for each contrast) with a minimum cluster size of $k = 15$ voxels. Abbreviations: H, hemisphere; BA, Brodmann area; CS, cluster size in the number of activated voxels; L, left; R, right; DL, dorsolateral, DM, dorsomedial; PFC, prefrontal cortex; TPJ, temporo-parietal junction; IFG, inferior frontal gyrus; and T, t-values for each given peak.

down cognitive control, and a 'social-DMN' source, specific for social cognition (Fig. 5B, C). For both sources, the overlap with the DMN is striking. Noticeably, a recent constructivist model of emotion suggests that the DMN may contribute to emotions and their regulation by creating meaning of ongoing sensations based on both represented previous experiences and particular context (Barrett and Satpute, 2013; Lindquist et al., 2012). One could thus speculate that Social-Reg, via the DMN, promotes a specific trajectory of emotion processing by accounting for social information (e.g., "I am here to help you"), serving as a 'safety signal' in the immediate context.

4.2. Attachment security and Social-Reg

Individual differences in attachment security were positively associated with both regulation success and brain activation in the OFC (Fig. 3). Attachment security reflects the propensity to establish intimate emotional bonds with others, manifested by the extent to which a person is willing to trust and rely on others for support (Collins and Feeney, 2000). Our data indicate that secure attachment is related to greater benefits from Social-Reg, consistent with previous suggestions that securely attached individuals are more sensitive to and reliant on the protection, support and guidance from others (Mikulincer and Shaver, 2008; Shaver and Mikulincer, 2007). Furthermore, research in psychotherapy has suggested that a client's sense of security in close relationships and in the relationship with the therapist will facilitate the therapeutic process and enhance therapeutic outcomes (Bowlby, 2005; Mikulincer et al., 2013). In line with this, a recent meta-analysis demonstrated that attachment security was significantly positively associated with treatment effects of psychotherapy (Levy et al., 2011).

Our brain data further suggest that the susceptibility to this form of social influence correlates with activity changes in the lateral OFC. The lateral OFC has been widely discussed in relation to emotion regulation as a key region of the cognitive control network (Canterberry and Gillath, 2013; Eippert et al., 2007), and is furthermore seen as a critical region for encoding attachment-relevant stimuli, such as one's own infant, romantic partner, or attachment-related words (Minagawa-Kawai et al., 2009; Vrtička and Vuilleumier, 2012). The observed correlation may indicate that attachment security facilitates both cognitive control and social relatedness specifically via the lateral OFC. Noticeably, no similar correlations for Self-Reg were found (Table S2), suggesting that individuals' attachment security specifically contributes to the effectiveness of Social-Reg.

4.3. Implications for psychotherapy and affective disorders

Concerning psychotherapy, interaction-based interventions are recognized as particularly powerful therapeutic tools in disorders hallmarked by emotion dysregulation, and basically rely on Social-Reg by the therapist (Barker and Pistrang, 2002; Cuijpers et al., 2013; DeRubeis et al., 2008). CBT, especially, represents one of the clear success stories in interaction-based interventions. Social-Reg is a cardinal technology of CBT, during which therapists instruct and guide clients to identify negative, self-destructive thoughts, and assist them to develop positive, adaptive thought patterns so as to improve their emotional state and equip them with the skills to better regulate their own emotions in the long run (Beck, 1997; Butler et al., 2006; Frewen et al., 2008). CBT has shown encouraging effects on reducing negative thinking, depressive feelings and anxious responses (Cuijpers et al., 2013; Park et al., 2014), and more importantly, people treated with CBT show improved competences in cognitive regulation as well as increases in PFC function (DeRubeis et al., 2008; Siegle et al., 2007). Our experimental design mimics the basic aspects of CBT. Outside the clinical context, the Social-Reg can also be used by friends and family to provide emotional support in the emotionally-challenging moment, without an outlook on the target's own regulatory abilities (Reeck et al., 2015).

The present design offers the means to assess immediate effects and brain mechanisms of a Social-Reg session with a psychotherapist. The current findings provide an account of how DMN-related neural mechanisms may underlie interaction-based psychotherapeutic interventions. Data also shed light on why such interaction-based interventions are only partially successful in some specific disorder conditions, as the DMN is highly impaired in most of these disorders, e.g., in autism and treatment-resistant depression (Assaf et al., 2013; Li et al., 2013; Lynch et al., 2013; Orosz et al., 2012; Sheline et al., 2009). Finally, the observed association between attachment security, regulation success, and the DMN suggests that the DMN and Social-Reg may provide a link between attachment insecurity and an increased risk for affective disorders (Hankin et al., 2005; Marganska et al., 2013; von dem Hagen et al., 2012). More specifically, persons who have problems relying on others might find it hard to profit from Social-Reg. The reduced capability of using social resources for emotion regulation, in turn, may explain the increased risk for emotion dysregulation, which is at the core of many affective disorders and associated with the DMN.

4.4. Conceptual and methodological issues

The present work represents the first investigation into the neural mechanisms of Social-Reg. Therefore, some conceptual and methodological issues are worth noting.

Social-Reg was launched via instructions that preceded emotional stimulation, in line with the definition of cognitive emotion regulation as an antecedent regulatory approach. Participants might have thus implemented these social instructions independently (i.e., in a self-regulatory way) at a later point in time (during picture presentation), which the present design cannot completely rule out. However, it is reasonable to assume that Social-Reg, in general, partly draws on self-regulation resources, as was also suggested by the regional overlap between Social-Reg and Self-Reg (Fig. 5). In fact, social- and self-regulation do not have an absolute boundary and occur in the overlapping intervals on a self-to-social continuum (Zaki and Williams, 2013). Social regulation is thus socially-induced, but eventually self-implemented, in most cases. In the present design, consistent with the definition of Social-Reg (i.e., offering targets alternative interpretations for emotionally evocative stimuli to minimize their distress, Reeck et al., 2015), the manipulation of Social-Reg configured the processes in which an expert initiated and guided the regulation by assigning precise reappraisal substrategies to participants who were asked to simply follow the instructions. In contrast, during Self-Reg, participants decided when to start the regulation and which particular tactic to use for each picture, based on the pre-experimental training. Crucially, Social-Reg, as revealed by our analysis, was supported not only by the typical cognitive control network associated with Self-Reg, but also by an additional network specifically related to social cognition. At the very least, the observed Social-Reg effects might be a rather conservative estimate of the actual effects of Social-Reg. Future studies, directly manipulating the level of social involvement in different types of socially-induced emotion regulation, are needed to confirm and supplement the current findings.

To establish a regulator–target relationship of trust and confidence, a psychotherapist was used as the regulator and introduced face-to-face to the participants prior to the experiment as an expert that can help them regulate their emotions. On the one hand, the relatively weak and temporary tie between the regulator and target might have reduced the effects of Social-Reg. In real life, it is hard to form a close connection between two strangers within a short time, while rapport is a main curative component in therapy (Horvath and Symonds, 1991; Martin et al., 2000). Thus, an established close relationship with a therapist or friend might result in an even more effective Social-Reg. On the other hand, the psychotherapist was more likely to be perceived as both warm and competent on an initial encounter, compared to an unfamiliar other, the two main traits responsible for a positive social perception

(Fiske et al., 2007). Nevertheless, the current study should only be taken as an approximation to real-life Social-Reg in psychotherapy. Follow-up studies are needed to assess whether and how the quality of a regulator–target relationship may alter the benefits of Social-Reg. To avoid possible gender and familiarity effects (McRae et al., 2008), the study sample included only female subjects, and Social-Reg instructions were communicated by an unfamiliar female psychotherapist. As such, the results cannot be generalized to male participants or social interactions between opposite-sex or familiar individuals. Similarly, as participants recruited in this study were healthy with sound Self-Reg abilities, Social-Reg in fact appeared less effective than Self-Reg. Future work could examine the generalizability of the study findings to other kinds of populations, especially clinical populations that are troubled with impaired Self-Reg abilities, such as major depression patients. Likewise, although the IAPS pictures used in the present study were effective at evoking aversive emotions, they have less ecological validity than stimuli derived from real-life experiences, such as personal memories or social interactions. Future studies can help assess the generalizability of the study findings to other types of emotionally-evocative stimuli.

5. Conclusion

The present study provides initial insights into the neural mechanisms of Social-Reg. Our results provide evidence for the specific involvement of the DMN in Social-Reg and its association with individual differences in attachment security. These findings are relevant for our understanding of affective disorders, such as the reduced susceptibility to social emotion regulation in depressed patients, which might be due to an impaired DMN. They may also help to understand the increased risk of individuals with low attachment security for affective disorders, which may also be due to an impaired DMN and deficient capabilities to use social resources for emotion regulation.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2016.04.015.

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Supplementary Data for

"How do you make me feel better? Social cognitive emotion regulation and the default mode network" by Xie, Mulej Bratec et al.

Supplementary Methods

Supplementary Analyses and Results

Supplementary Figures

Supplementary Tables

Supplementary Methods

1. Experimental procedure

In the Social-Reg task, participants first met the psychotherapist, who was introduced as an expert that would accompany and assist them in regulating their emotions during the task. Participants were then trained to follow the psychotherapist's instructions while viewing negative pictures. They were presented with the same paradigm, but observed pre-recorded videos of a fellow female colleague instead of the psychotherapist. They practiced until they were confident that they could understand and follow the instructions in the videos without effort. Participants met the psychotherapist again immediately before scanning and were reminded that she would be in an adjacent room and give them on-line instructions during scanning. They were also told that they should entrust the psychotherapist with the regulation process and should not use any other strategies to change their emotions. The scanning took about 1 hour, with a short anatomical scan between two half-hour runs. The practice videos and pictures were not used in the experiment. After the entire experiment, participants completed an interview to confirm whether they believed the cover story and engaged in the task.

The Self-Reg task started with a training session, to teach participants how to generate and implement concrete distancing strategies by themselves while viewing negative pictures, in preparation for scanning. The experimenter guided and shaped the specific strategy based on feedback from the participant to ensure that they could employ the distancing strategy successfully. Participants were reminded that they should only use distancing (rather than, for example, closing their eyes or thinking about something positive) to down-regulate their emotions. The training and pre-scanning preparation lasted for about 35 minutes. After training, participants completed the 1-hour-long scanning. Training pictures were not used in the experiment. After scanning, participants were asked to describe the specific regulation strategy/strategies they used during scanning to confirm whether they correctly followed the instructions.

2. Experimental materials

Emotional pictures: To elicit aversive emotions, 160 negative pictures were selected from the International Affective Picture System (IAPS, Lang et al., 2005), and assigned to four experimental conditions (i.e., Social-Reg, Social-Look, Self-Reg and Self-Look), based on normative ratings of valence and arousal (valence: $M = 2.22$, $SD = 0.47$; arousal: $M = 6.07$, $SD = 0.61$) (all pictures are listed below). Two one-way ANOVAs showed that the pictures of the four experimental conditions did not differ in valence ($F_{3, 159} = 0.41$, $p > 0.70$) or arousal ($F_{3, 159} = 0.06$, $p > 0.95$). The picture presentation order was random and differed for each participant.

IAPS picture list

9185, 2981, 3053, 6313, 9630, 3530, 9620, 3180, 9301, 1111, 6370, 3015, 3140, 2800, 3069, 9050, 9904, 2710, 9500, 3101, 3181, 3220, 9909, 6243, 3195, 9325, 9184, 9163, 3001, 3120, 9425, 9810, 3400, 2661, 3103, 3062, 9920, 2141, 3059, 3063, 3110, 9921, 3150, 9423, 3060, 9414, 3068, 9412, 9008, 3191, 4664.2, 9435, 6350, 9623, 3213, 3230, 6520, 9295, 2375.1, 8230, 9910, 9901, 9321, 3019, 9253, 9040, 9187, 3225, 9599, 9600, 3131, 9611, 3130, 9410, 9905, 3215, 9140, 6022, 6231, 2205, 3160, 9400, 9415, 9911, 9007, 3010, 3170, 9322, 3051, 9421, 9900, 6838, 3550, 6021, 6571, 3301, 2683, 9181, 3212, 8485, 6550, 6563, 3100, 9635.1, 2730, 2352.2, 3185, 6212, 9183, 3071, 2717, 3016, 9800, 9075, 3005.1, 1930, 3102, 2095, 6821, 9902, 9420, 2799, 3064, 9908, 3266, 2053, 3061, 3500, 2691, 3080, 9250, 6830, 9571, 6315, 9940, 9433, 9428, 9903, 9941, 9006, 3030, 3350, 3261, 6300, 9326, 3000, 6560, 2703, 3168, 9252, 9405, 9332, 9043, 9300, 9560, 7380, 3017, 9570, 9254, 6230

Social-Reg instructions: 33 sentences were used as instructions for the Social-Reg task, 22 for the Reg and 11 for the Look condition (listed separately below). The psychotherapist spoke each sentence several times, to resemble natural communication and prevent repetition of non-verbal movements. Totally, 80 unique video clips were created for each of the Reg and Look conditions, one for each trial. The instructions were presented in a pseudorandom order, such that no repetitions of the same sentence were presented consecutively.

Social-Reg instructions list

22 Sentences Used in the Social-Reg Condition (*English Translation*)	
Sie wissen, Sie sind nicht betroffen.	*You know that you are not affected.*
Denken Sie daran, dass Sie hier sicher sind.	*Keep in mind that you are safe here.*
Vergessen Sie nicht, die Bilder haben nichts mit Ihnen	*Don't forget, the pictures are not related to you.*

zu tun.	
Vergessen Sie nicht, Sie sind nicht auf den Bildern dargestellt.	*Don't forget, you are not depicted in the pictures.*
Das hier ist eine Untersuchung, nicht die Realität.	*This is just an experiment, not reality.*
Denken Sie daran, dass die Bilder nur gestellt sind.	*You know that the scenes are just staged.*
Sie wissen, die Bilder betreffen Sie nicht.	*You know that these pictures do not affect you.*
Weder Sie noch Ihre Familienangehörigen sind betroffen.	*Neither you nor your relatives are involved.*
Sorgen Sie sich nicht, Sie sind hier sicher.	*Don't worry, you are safe here.*
Sie müssen keine Angst haben, die Bilder sind gestellt.	*You don't have to be afraid, the pictures are staged.*
Erschrecken Sie nicht, die Bilder sind nur gestellt.	*Don't be scared, the pictures are just staged.*
Sie sind in Sicherheit, Ihnen kann nichts passieren.	*You are safe, nothing bad can happen to you.*
Auf den Bildern sind Szenen dargestellt.	*The pictures depict scenes.*
Die Bilder haben nichts mit ihrem Leben zu tun.	*The pictures don't concern your life.*
Sie und Ihre Familie sind in Sicherheit.	*You and your family are safe.*
Sie wissen, dass die Bilder nichts mit der Realität zu tun haben.	*You know that the pictures are not related to reality.*
Sie wissen, dass Sie an einer Untersuchung teilnehmen.	*You know that you are simply participating in an experiment.*
Sie wissen, die Bilder sind nicht real.	*You know that the scenes in the pictures are not real.*
Sie wissen, dass Sie hier sicher sind.	*You know that you are safe here.*
Atmen Sie ruhig weiter, Sie sind hier sicher.	*Keep breathing calmly, you are safe here.*
Denken Sie daran, die Bilder haben nichts mit Ihrem Alltag zu tun.	*Keep in mind that the pictures are not related to your everyday life.*
Denken Sie daran, die Bilder haben nichts mit Ihrem Situation zu tun.	*Keep in mind that the pictures have nothing to do with your situation.*

11 Sentences Used in the Social-Look Condition (*English Translation*)	
Schauen Sie das Bild einfach an.	*Simply look at the picture.*
Schauen Sie das Bild an.	*Look at the picture.*
Verdeutlichen Sie sich den Inhalt des Bildes.	*Pay attention to the picture's content.*
Machen Sie sich den Inhalt des Bildes klar.	*Bring the content of the picture to your mind.*
Lassen Sie Ihre Gefühle zu.	*Experience your feelings.*
Lassen Sie Ihre Gefühle beim Betrachten des Bildes zu.	*Experience your feelings when looking at the picture.*
Ändern Sie Ihre Gefühle nicht.	*Don't change your feelings.*
Lassen Sie die Gefühle, die das Bild auslöst, zu.	*Experience the feelings induced by the picture.*
Schauen Sie sich das Bild an.	*Look at the picture.*
Machen Sie sich klar, was auf dem Bild dargestellt ist.	*Make what is shown on the picture clear to you.*
Seien Sie sich im Klaren über die Bedeutung des Bildes.	*Be aware of the picture's meaning.*

Supplementary Analyses and Results

1. Group ICA to identify the DMN

Resting-state fMRI data were acquired before each task (Social- and Self-Reg) on the same sample (22 healthy female participants) with the same scanning parameters (see Materials and Methods in the main text). Altogether, 480 volumes were acquired. Data were preprocessed by SPM8, including motion correction, spatial normalization (resulted voxel size = 3×3×3 mm) based on unified segmentation of T1-weighted images, and smoothing (FWHM = 8mm). Preprocessed data were decomposed into 75 spatial independent components within a group-ICA framework, based on the Infomax algorithm and implemented by GIFT (GIFT v1.3h; http://mialab.mrn.org/software/#gica) (Allen 2013). In detail, data were temporally concatenated and reduced by a two-step principal component analysis (PCA), followed by spatial independent component estimation with the Infomax algorithm. To ensure stability of the estimated components, ICA was repeated 100 times (with ICASSO). Group ICA provided a set of group-level independent components, which were then back-reconstructed into single subject space. Each back-reconstructed component consisted of a whole-brain intensity map reflecting the component's functional connectivity pattern across the entire space, and an associated time course reflecting the component's activity across time.

DMN identification was performed by a spatial cross-correlation between the generated ICA maps and four DMN templates described in Allen et al. (2011). Four independent components, which exhibited the largest correlation coefficient with each DMN sub-network template, were selected (Figure S4A). To determine voxel-wise statistics, one-sample t-tests with a gray-matter mask were carried out for each component, with a rigorous multiple comparison correction (voxel-wise $p < 0.05$, FWE corrected) and an extent threshold ($k = 60$ voxels). The significant results were merged into a DMN map (Figure S4B). The identified DMN map included dorsal and ventral portions of the medial prefrontal cortex, the posterior cingulate cortex extending into the precuneus, and bilateral parietal and posterior temporal areas around the temporo-parietal junction.

2. Specificity of the correlations between attachment security and Social-Reg

To confirm the specificity of the correlations between Social-Reg and attachment security, we also examined the correlations between Self-Reg and attachment security. We found that: (i) at the behavioral level, the correlation between attachment security and Self-Reg success was not significant (r = -0.043, p > 0.1), and that there was a trend towards a difference between this coefficient and the one for Social-Reg (r = 0.42; z = 1.39, p = 0.082); (ii) the activation increases during Self-Reg (i.e., averaged ß-values of each significant cluster in the contrast Self-Reg > Self-Look, p < 0.05, FWE corrected) were not correlated with attachment security (-0.104 < r < 0.301, all p > 0.1; see Table S2); (iii) the bilateral OFC activation (i.e., averaged ß-values of the OFC, as identified by the AAL template, in the contrast Self-Reg > Self-Look, p < 0.001, uncorrected) was not correlated with attachment security (r = -0.053, p > 0.4), and that there was a trend towards a difference between this coefficient and the one for Social-Reg (r = 0.44; z = 1.49, p = 0.068). Results suggest that the observed correlation patterns were specific for Social-Reg.

3. Task order effects

Social- and Self-Reg tasks were conducted successively for each participant. To rule out any possible differences in results induced by the task order, participants were separated into two groups according to their actual task order in the experiment (i.e., Group 1: Social-Reg task -> Self-Reg task, including 9 participants; Group 2: Self-Reg task -> Social-Reg task, including 10 participants). Two-sample t-tests were then conducted to test whether the effect of Reg > Look differed between the two groups in either the Social- or Self-Reg tasks.

At the brain level, whole-brain analyses showed no significant between-group differences for the effect of Reg > Look in either the Social- or the Self-Reg task, at both the predefined statistical threshold (p < 0.05, FWE cluster-corrected) and a more liberal threshold (p < 0.001, uncorrected). We further restricted the analysis to the DMN key regions that were recruited by Social-Reg (i.e, the precuneus, the medial frontal cortex and the temporo-parietal junction), and still found no between-group differences for the effect of Reg > Look in either the Social- or the Self-Reg task (p < 0.05, FWE cluster-corrected). Results therefore show that, at the brain level, the task order did not affect the spatial extent of the network

supporting Social-Reg, indicating that no matter which task the participant did first, they all exhibited a consistent brain activation pattern in both the Social- and the Self-Reg tasks.

At the behavioral level, we examined whether either the Self-Reg or the Social-Reg success might have been affected by the task order (i.e., might have been augmented by the preceding task when either task was performed second). Regarding Self-Reg, analysis showed that Self-Reg success did not differ between the two groups (t_{17}= 1.58, $p > 0.05$, d = 0.77), indicating that completing the Social-Reg task first did not augment the Self-Reg success in Group 1. This is reasonable considering the Social-Reg paradigm. Despite the fact that our Social-Reg implementation resembled the Social-Reg used in psychotherapy, the goal of which is to eventually improve the patient's Self-Reg ability, it is reasonable to assume that a single Social-Reg session cannot have a significant impact on Self-Reg, especially in young, healthy individuals with sound reappraisal skills to start with. Regarding the Social-Reg success, results showed that Group 2 participants, who first completed the Self-Reg task, had a higher Social-Reg success than Group 1 participants who started with the Social-Reg task (t_{17}= 4.29, $p < 0.001$, d = 2.08). There are two noncompeting possibilities. First, it could be that the Self-Reg task facilitated the effectiveness of Social-Reg, such that previous experiences of reappraisal might have assisted participants in better understanding and recognizing reappraisal instructions in the Social-Reg task. Similar findings have been reported in relation to psychotherapy, where non-disorder-specific training of general emotion regulation skills has been shown to improve the effects of CBT-based treatments (Berking et al., 2008; 2015). Second, it is also possible that participants in Group 2, who first (successfully) regulated negative emotions by themselves in the same context, found it more difficult to completely entrust the psychotherapist with the regulation in the second session a week later and perhaps partly enhanced the regulation by themselves when needed. This result does, however, not affect either the effectiveness or the distinctiveness of Social-Reg in the present study. First, Social-Reg success was significant in both task-order groups, including Group 1 that started with Social-Reg (both $t_{17} > 6.0$, $p < 0.001$, and $d > 1.02$), showing that Social-Reg was effective regardless of the task order. Second, the distinct network supporting Social-Reg, including DMN regions, was evident in both task-order groups, including Group 1 that started with Social-Reg, showing that the task order had no

effect on the main finding of this study.

4. Impact of preceding events on picture presentation

When comparing Social- and Self-Reg effects on brain activity during the picture presentation phase, a potential confound might have occurred due to carry-over effects from preceding events, i.e., the instruction (6 s) and anticipation (6 s) phases. To control for these potential carry-over effects from the preceding events, a new second level GLM analysis was performed based on different contrast images from the first level analysis. While the original contrast images of the first level analysis were based on the contrast picture vs. baseline in the initial analysis, the control analysis included first level contrast images defined by the contrast picture vs. instruction-anticipation (combined instruction and anticipation regressors). The control analysis thus focused on brain activity during picture presentation, controlled for any activation induced by the instruction or anticipation phases. Individual contrast images were subjected to a flexible factorial model with the factors instruction (Reg/Look) and task (Social/Self), mirroring the initial analysis.

The contrast Social-Reg > Social-Look identified activations in the bilateral dorsolateral and dorsomedial PFC, bilateral inferior parietal cortex, OFC, dorsal ACC, and precuneus/PCC ($p < 0.05$, FWE cluster-corrected), covering all clusters of the initial analysis focused on picture presentation (Figure S6A). In particular, the interaction contrast (Reg > Look)$_{Social}$ > (Reg > Look)$_{Self}$ also yielded a highly similar activity pattern as the initial analysis focused on picture presentation ($p < 0.005$, Figure S6B). The data confirm that the Social-Reg activity observed during picture presentation was not confounded by carry-over effects from preceding events.

Supplementary Figures

Figure S1

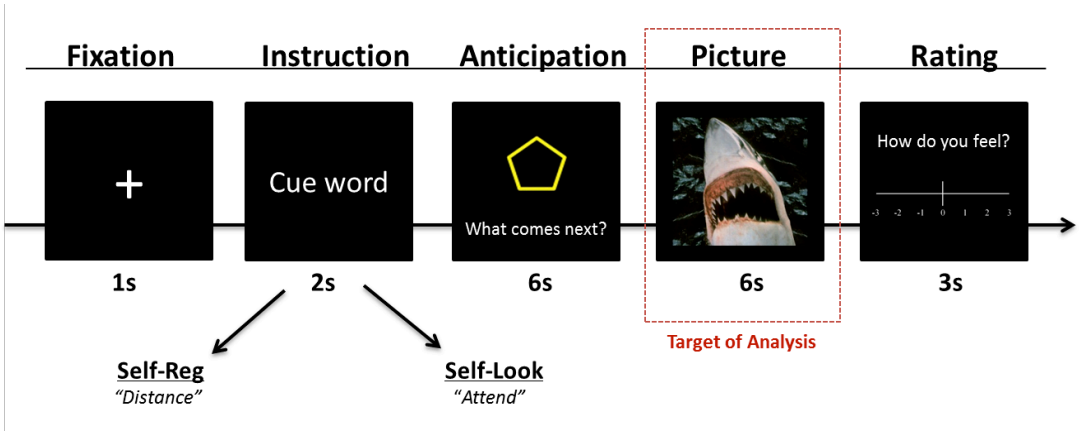

Figure S1: Trial structure of the Self-Reg task

The paradigm fully resembled that of the Social-Reg task, with the instruction phase duration reduced to 2 s, for presenting the cue word. Participants were asked to down-regulate their emotions by using self-distancing ('Distance') or to simply attend to the pictures ('Attend') while viewing the negative pictures.

Figure S2

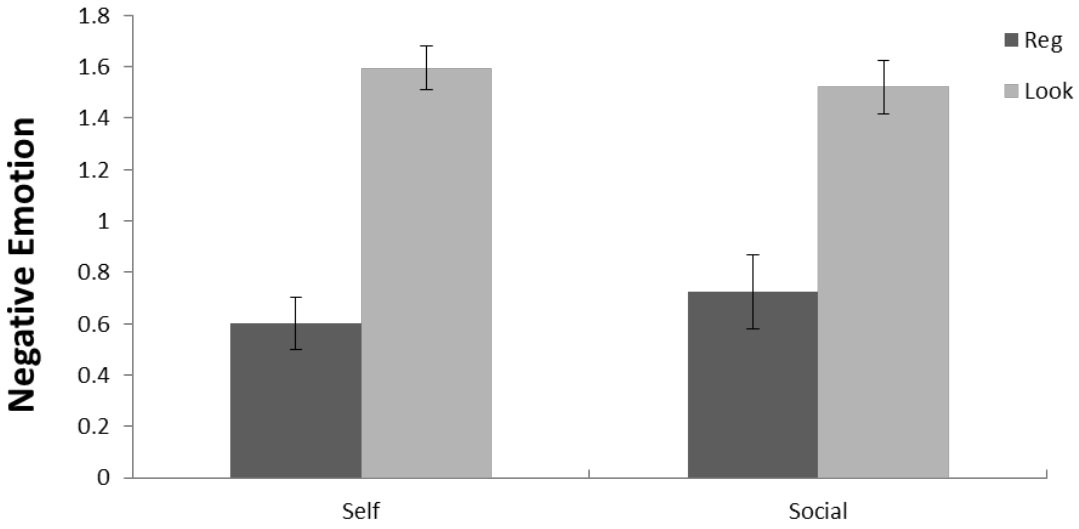

Figure S2: Emotional rating scores results

To evaluate the effects of regulation on emotional rating scores, paired t-tests were conducted. Data showed that negative emotions were significantly lower in the Reg condition compared to the Look condition, in both the Social-Reg (t_{18}= 8.55, $p < 0.001$, $d = 1.44$) and the Self-Reg task (t_{18}= 10.29, $p < 0.001$, $d = 2.38$). An additional planned t-tests, comparing Social-Reg (Social-Reg – Social-Look) and Self-Reg success (Self-Reg – Self-Look), showed that Self-Reg led to a greater reduction in rating scores than Social-Reg ($t_{18} = 2.47$, $p < 0.05$, $d = 1.16$). Absolute values of the rating scores are shown, and error bars represent 95% confidence intervals.

Figure S3

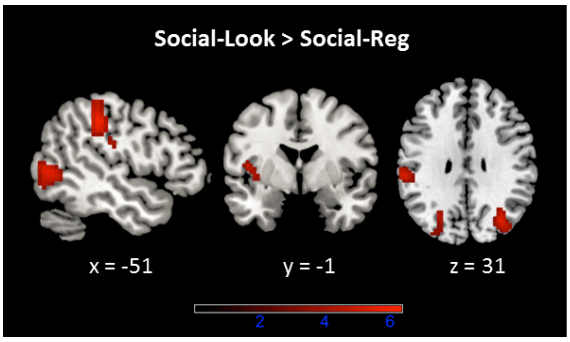

Figure S3: Areas modulated by Social-Reg

Brain areas modulated by Social-Reg were examined by the contrast Social-Look > Social-Reg. All $p < 0.05$, FWE cluster-corrected, except for the left insula (peak at [-39 -1 1], k=17 voxels; survived at the height threshold $p < 0.001$).

Figure S4

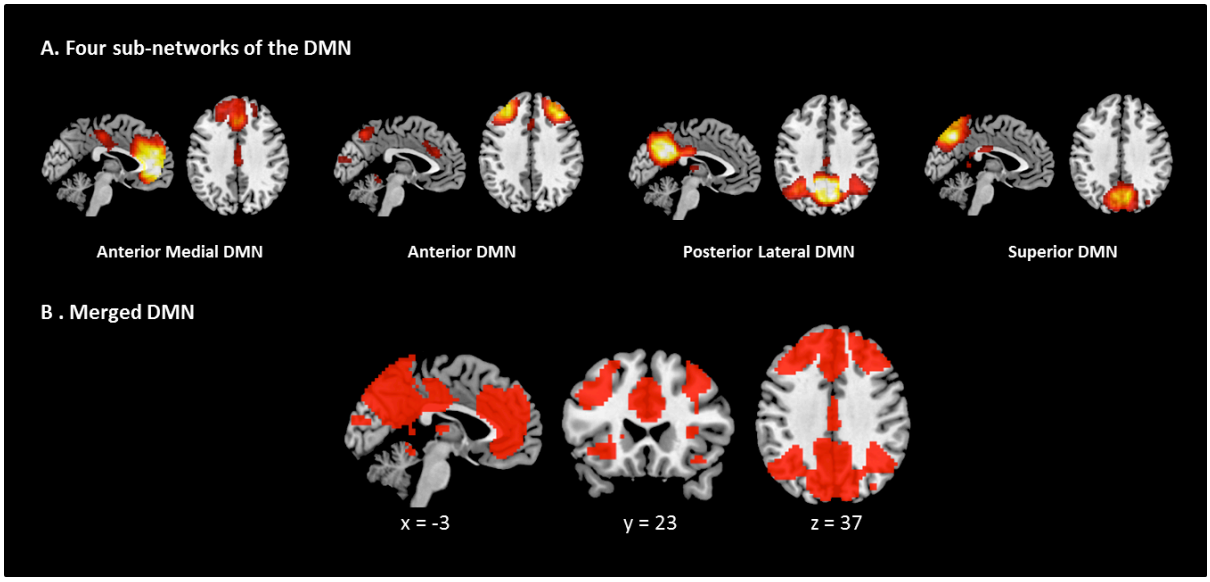

Figure S4: DMN as identified by the resting-state fMRI data

(**A**) Four independent components were identified based on a group ICA and DMN sub-network templates (Allen et al., 2011). Spatial maps are based on all participants and plotted as t-statistical maps ($p < 0.05$, FWE voxel-corrected). (**B**) Significant results were merged into a single map to represent the DMN as a whole.

Figure S5

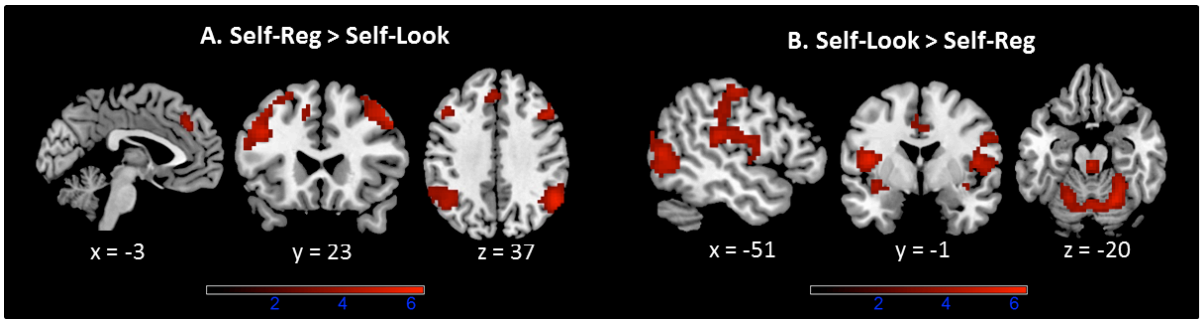

Figure S5: Areas recruited and modulated by Self-Reg

(**A**) Brain areas recruited by Self-Reg were examined by the contrast Self-Reg > Self-Look. (**B**) Brain areas modulated by Self-Reg were examined by the contrast Self-Look > Self-Reg. Images are displayed at $p < 0.05$, FWE cluster-corrected threshold.

Figure S6

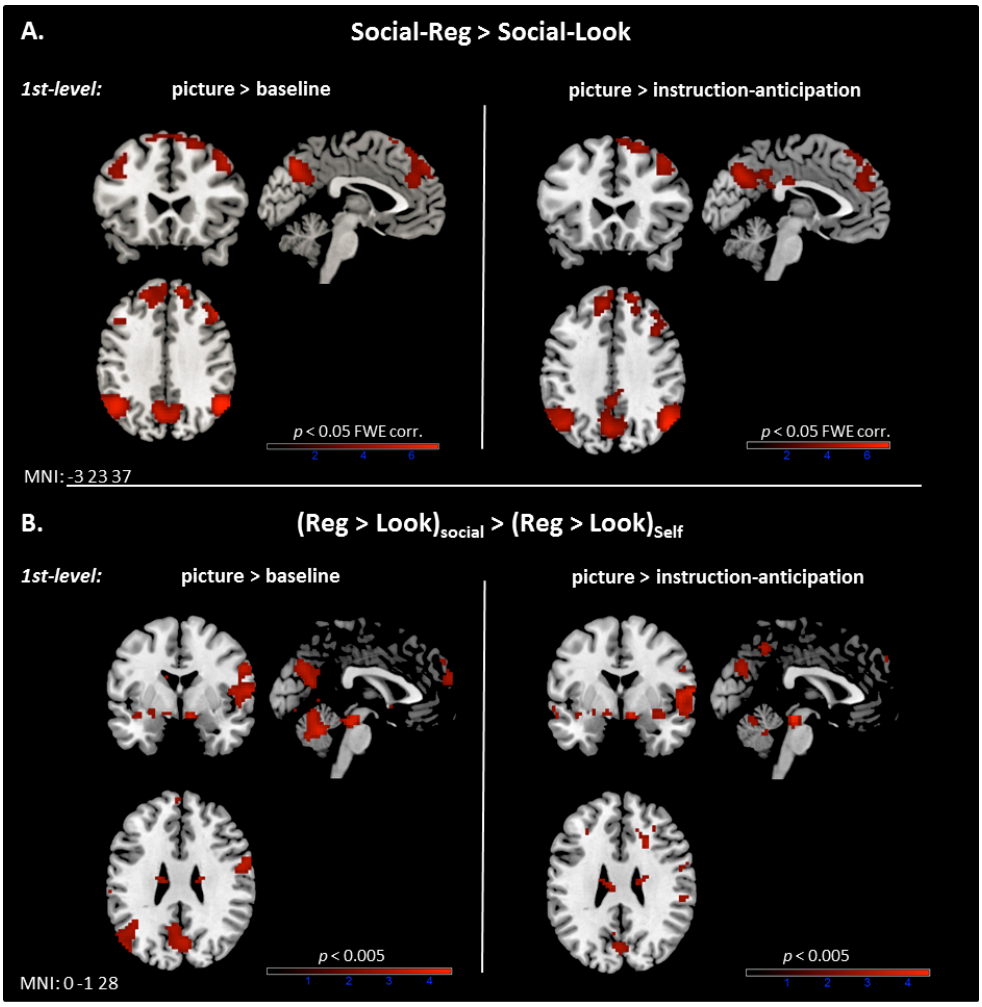

Figure S6: Social-Reg activation controlled for potential carry-over effects of preceding events

(**A**) Activations revealed by the contrast Social-Reg > Social-Look, based on the individual contrast images from the original first-level analysis (left panel) and the adapted first-level analysis with the effects of preceding events regressed out (right panel). Images are displayed at $p < 0.05$, FWE cluster-corrected threshold. (**B**) Activations yielded by the interaction contrast $(\text{Reg} > \text{Look})_{\text{Social}} > (\text{Reg} > \text{Look})_{\text{Self}}$, based on the individual contrast images from the original first-level analysis (left panel) and the adapted first-level analysis with the effects of preceding events regressed out (right panel). Images are displayed at a voxel-wise threshold $p < 0.005$, with a cluster extent of 15 voxels.

Supplementary Tables

Table S1: Social-Reg, regulation success, and attachment: correlation analyses

Brain regions	Regulation Success		Attachment Security	
	r	***p***	***r***	***p***
Social-Reg > Social-Look				
R_Inferior parietal	0.269	0.133	0.239	0.162
L_Inferior parietal	**0.734**	**0.0001**	0.375	0.057
Precuneus	**0.441**	**0.029**	0.137	0.288
L_Middle frontal (DLPFC)	0.048	0.423	0.154	0.264
Superior frontal (DMPFC)	0.117	0.317	0.149	0.271
Bilateral orbitofrontal (OFC)	0.068	0.391	**0.444**	**0.028**
Medial frontal (DMPFC)	0.093	0.353	0.069	0.389
Bilateral superior and middle frontal (DLPFC)	0.107	0.331	0.141	0.283

Note: Averaged ß-values for 5 significant clusters in the contrast Social-Reg > Social-Look were extracted and correlated with corresponding behavioral scores using Pearson's correlation with a significance level of $p < 0.05$, uncorrected. Since the superior frontal cortex cluster covered several prefrontal subregions, we divided it into 3 subregions following the Automated Anatomical Labeling (AAL) templates to improve analysis specificity. Significant values are shown in bold. Abbreviations: L, left; R, right; DL, dorsolateral, DM, dorsomedial; OFC, orbitofrontal cortex; and PFC, prefrontal cortex. The significant correlations are displayed in bold letters.

Table S2: Self-Reg, regulation success, and attachment: correlation analyses

Brain regions	Regulation Success		Attachment Security	
	r	***p***	***r***	***p***
Self-Reg > Self-Look				
Inferior parietal	0.066	0.394	0.134	0.293
Middle frontal (DLPFC)	-0.239	0.163	0.123	0.309
Inferior parietal	0.100	0.342	0.301	0.106
Inferior frontal (DLPFC)	-0.286	0.118	0.292	0.113
Superior medial frontal (DMPFC)	-0.094	0.351	-0.104	0.336
Bilateral orbitofrontal (OFC)	-0.289	0.115	-0.053	0.414

Note: Averaged ß-values for 5 significant clusters in the contrast Self-Reg > Self-Look were extracted and correlated with corresponding behavioral scores using Pearson's correlation with a significance level of $p < 0.05$, uncorrected. The lateral orbitofrontal cortex (OFC, in italics) was identified following the Automated Anatomical Labeling (AAL) template, to confirm that the correlation between the OFC activation and attachment security was specific for Social-Reg and not for emotion regulation in general. Abbreviations: L, left; R, right; DL, dorsolateral, DM, dorsomedial; and PFC, prefrontal cortex.

Table S3: Areas recruited by Self-Reg

Brain region	H	BA	CS	MNI coordinates			*T*
				x	y	z	
Self-Reg > Self-Look							
Inferior parietal	R	39/40	343	54	-55	49	6.32
Middle frontal (DLPFC)	R	9	176	45	20	43	6.05
Inferior parietal	L	40	306	-42	-58	55	5.82
Supramarginal	L	40		-60	-49	31	3.58
Inferior frontal (DLPFC)	L	45/48	212	-42	26	28	5.37
Middle frontal (DLPFC)	L	6/9		-39	8	55	5.06
Superior medial frontal (DMPFC)	L	8/32	81	-3	38	34	4.27
Superior frontal (DMPFC)	L	32		-12	20	43	3.89

Note: Results are derived from a voxel-wise *t*-test for the contrast Self-Reg > Self-Look. All results are given at a cluster-wise threshold of $p < 0.05$, FWE corrected, based on a voxel-wise threshold of $p < 0.001$ and a minimum cluster size $k = 70$ voxels. Abbreviations: H, hemisphere; BA, Brodmann area; CS, cluster size in number of activated voxels; L, left; R, right; DL, dorsolateral, DM, dorsomedial; PFC, prefrontal cortex; and T, t-values for each given peak.

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5

Project 4: Social Context Affects Distinct Types of Emotional Activity in Subregions of the Human Insula

The current chapter includes a research manuscript entitled “Social context affects distinct types of emotional activity in subregions of the human insula”. Using a novel paradigm, it provides a first account on how social emotion modulation affects two distinct types of neural activity – emotional response- and aversive prediction error-related activity – in the left and right anterior and posterior insula parts, and thus illuminates the anterior-posterior gradient hypothesized in the human insula. The manuscript is currently unpublished.

Contributions:

Authors: *Satja Mulej Bratec, Xiyao Xie, Leonhard Schilbach, Gabriele Schmid, Claus Zimmer, Afra Wohlschläger, Valentin Riedl, Christian Sorg*

The author of this thesis shares the first authorship of the manuscript with Xiyao Xie. **S.M.B.**, X.X. and C.S. conceived the experiment, with the help of C.Z. **S.M.B.** and X.X., under the supervision of C.S., filmed G.S. to create the social modulation videos used in the experiment. **S.M.B.** and X.X. together conducted behavioural and fMRI data acquisition, with the help of G.S. (the psychotherapist). **S.M.B.** and X.X. analysed the behavioural and the neuroimaging data, with some help from A.W. and V.R., supervised by C.S. **S.M.B.** wrote the manuscript, which was revised by X.X. The writing was supervised by C.S., and the manuscript was commented on and additionally revised by L.S.

Social context affects distinct types of emotional activity in subregions of the human insula

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Abstract

The human insula is one of the most differentially expanded brain parts to support complex human socio-emotional behavior; however, the mechanisms underlying such behavior in the insular cortex are incompletely understood. We investigated differential effects of social context change during aversive conditioning on insula activity for 3 contrasting dimensions: anterior versus posterior insula (AI and PI, respectively), due to the posterior-to-anterior insular processing hierarchy and functional gradient; aversive prediction error- versus aversive stimulus-related activity, two functionally distinct types of activity relevant for emotional behavior; and right versus left insula, based on the proposed differential insular control of the sympathetic and parasympathetic nervous systems. Results confirmed a three-fold dissociation between signal types and insula subregions: social presence reduced aversive stimulus-related activity only in the PI but not the AI; aversive prediction error-related activity was increased during social presence only in the AI but not the PI; and the social presence effect on aversive prediction error activity was positively associated with aversive learning in the right AI, but negatively in the left AI. Findings provide new insights into both the effects of social presence and the mechanisms supporting socio-emotional behavior in the human insula.

Introduction

The human insular cortex is one of the most differentially expanded brain regions, compared with other primates (Bauernfeind et al., 2013), making it a prime candidate to support complex social and emotional behavior (Craig, 2009; Lamm & Singer, 2010). Ample work has underlined the importance of insula in detecting salient environmental events, as well as the disparate roles of insula subregions in marking these events for further processing to maintain optimal socio-emotional functioning (Bauernfeind et al., 2013; Kurth, Zilles, Fox, Laird, & Eickhoff, 2010; Menon & Uddin, 2010).

For instance, anterior insula (AI) is known to be involved in complex emotional and social processing, information integration, and emotional awareness (Craig, 2009; Gu, Hof, Friston, & Fan, 2013; Hogeveen, Bird, Chau, Krueger, & Grafman, 2016; Kelly et al., 2012; Kurth et al., 2010; Lamm & Singer, 2010; Singer, Critchley, & Preuschoff, 2009). More specifically, AI is seen as the region that detects and integrates information about salience from all relevant conditions in a given moment to support awareness (Craig, 2009; 2010; Gu et al., 2013; Seth, 2013). The ventral AI has been implicated in complex social emotions (Lamm & Singer, 2010) and is known to contain von Economo neurons (i.e., large projection neurons specific to few socially highly developed species) (Allman et al., 2010). AI has furthermore been associated with various types of prediction errors, such as risk prediction errors (Bossaerts, 2010; Preuschoff, Quartz, & Bossaerts, 2008; Singer et al., 2009), interoceptive prediction errors (Gu et al., 2013; Paulus & Stein, 2006; Seth, 2013; Seth, Suzuki, & Critchley, 2012), and aversive prediction errors (i.e., prediction errors associated with aversive emotional events in the context of associative learning) (Garrison, Erdeniz, & Done, 2013; Kim, Shimojo, & O'Doherty, 2006; Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006; Seymour et al., 2004). Prediction errors, in general, represent a mismatch between prior expectations and reality, and appear to be a universal computation across the brain (Clark, 2013; Friston, 2005; Ouden, Kok, & de Lange, 2012). In the context of associative learning, prediction errors serve as teaching signals that drive motivated behavior, by providing us with information on whether and how much to adapt our behavior (Pearce & Bouton, 2001; Rescorla & Wagner, 1972; Schultz & Dickinson, 2000).

While AI supports higher-order integrated representations of interoceptive and emotional states and encodes various types of prediction errors, the posterior insula (PI), in contrast, supports primary representations of interoceptive states and feelings (Craig, 2009; Gu et al., 2013; Lamm & Singer, 2010; Seth, 2013). The PI has been repeatedly involved in regulating homeostatic states and physiological reactivity and to salient stimuli (Bauernfeind et al., 2013; Craig, 2003; Kurth et al., 2010; Menon & Uddin, 2010). Moreover, the representation of one's body state created by the PI is essential for generating subjective feelings and emotional awareness in the AI (Bauernfeind et al., 2013; Menon & Uddin, 2010). Functional differences between PI and AI and the hierarchical organization of the insula represent a posterior-to-anterior gradient in the human insula, with increasing processing complexity toward AI (Craig, 2009; 2011; 2010).

In addition, an emotional asymmetry between the right and left AI has been proposed, such that the right AI is preferentially involved in aversive emotions, due to the right-sided control of the sympathetic nervous system, while the left AI is predominantly relevant for positive emotions, in line with the left-centered parasympathetic nervous system control (Craig, 2009; 2005; 2010). However, despite elaborate theoretical and empirical work, our mechanistic understanding of the right and left AI and PI function is still incomplete, particularly concerning the distinction of aversive prediction error and aversive stimulus processing along the insula in socio-emotional contexts.

Previous studies demonstrated that insula activity can be targeted by manipulating the social context in the framework of aversive emotional processing (Eisenberger, 2013; Eisenberger et al., 2011; Younger, Aron, Parke, Chatterjee, & Mackey, 2010). Combining this with an established Pavlovian conditioning paradigm with varying conditioned-unconditioned stimulus contingencies, the current study investigated whether the social presence of a trustworthy other would target AI and PI regions differently, by modulating different types of activity in the insula subregions. We hypothesized that a change in the social context from 'alone' to 'social' would only affect stimulus-related activity in the PI (but not AI), while only modulating

prediction error-related activity in the AI (and not PI) (Craig, 2009; Gu et al., 2013; Seth, 2013). We further expected that the latter effect would be differentially associated with social context effects on learning performance in the right and left AI, due to the involvement of right and left AI in aversive and positive emotions, and the control of the sympathetic and the parasympathetic nervous systems, respectively (Craig, 2009; 2005; 2010).

Materials and Methods

Participants

Twenty-two healthy subjects (all female, mean age = 24.8 years, SD = 2.4 years) participated in the experiment, all native German speakers, right-handed, with normal or corrected-to-normal vision, and no history of neurological or psychiatric disorders, or intake of psychotropic medication. Two participants were excluded from further analysis due to excessive head movement during imaging (translation > 2 mm, rotation > 2°), and another two due to inadequate performance in the learning task. Owing to previous reports of gender differences regarding socio-emotional processing, only female subjects were tested (Eagly & Wood, 2013; McRae, Ochsner, Mauss, Gabrieli, & Gross, 2008; Nolen-Hoeksema, 2012; Whittle, Yücel, Yap, & Allen, 2011). After completion, participants received a financial reward for their participation. Written informed consent from all participants was obtained and the study was approved by a local ethics committee (Technische Universitaet Muenchen).

Experimental Design and Tasks

The conditioning paradigm closely resembled that of a previous study (Mulej Bratec et al., 2015). A trial started with a fixation cross (1 s), after which the 'Instruction' was presented: the word 'Attend' for trials without a psychotherapist (Alone; 2s) and a video of a psychotherapist for supportive social presence trials (Social; 5 s). Then, a CS (blue square or yellow pentagon) was presented (6 s) and during the first 3 s of CS presentation, participants indicated whether a negative picture or no picture would follow the CS via a button press. The US (6 s) was a negative picture from the International Affective Picture System (Lang, Bradley, & Cuthbert, 2008), shown on 50% of the trials (Paired trials). The picture set was balanced for arousal

and valence across Alone and Social conditions. Next, participants had 3 s to indicate their emotional state via a button press on a scale from -3 to 3 (increments of 1; set to 0 on each trial). The inter-trial interval lasted for 4 ± 2 s. Analysis of the current study focused on brain activity during US presentation, i.e., during the induction of aversive emotions. Each participant completed both Alone and Social runs, on different days, with the run order counterbalanced across subjects.

The Social run was inspired by previous studies on social support (Coan, Schaefer, & Davidson, 2006; Eisenberger et al., 2011; Younger et al., 2010), but was adapted to resemble a more realistic social interaction with an unknown but trustworthy individual. Each trial in the Social run started with a 5 s video of a female psychotherapist (G.S.), whom participants briefly met and interacted with before the experiment. She wore the exact same clothes and haircut as in the videos and participants were told that sitting in the scanner-adjacent room, the psychotherapist will have the opportunity to briefly speak to them at the beginning of each trial. Her 'instructions' were variations of the phrases 'Please attend to the pictures.' and 'Do not try to alter your emotions when looking at the pictures.' At the end of the experiment (after both runs), participants filled out a short post-scanning interview, which confirmed that all participants believed our cover story regarding the online presence of the psyhotherapist. In the Alone run, on the other hand, prompted by the word 'Attend', participants were asked to attend to the images they were presented with without actively trying to change the evoked emotions. Both Alone and Social runs thus resembled an 'attend' or 'no regulation' condition of a typical emotion regulation experiment.

The two experimental runs (Alone and Social) consisted of 80 trials each, with an equal proportion (40 trials) of CS1 and CS2 trials. A pseudorandom CS event train was used and the same CS could not occur on more than two consecutive trials. An average reinforcement probability of 50% resulted in 40 Paired and 40 non-Paired trials in each run. Furthermore, CS1 and CS2 were followed by an equal number of Paired trials (i.e., 20) in each run. The sine waves were used as threshold functions fort the trial sequence. A trial was Paired or non-Paired when a random number

drawn from the amplitude range was below or above the threshold function, respectively.

The CS-US contingency fluctuated throughout each run (low-frequency sine-wave function, with 1.75 and 1.5 cycles for CS1 and CS2, respectively) (Mulej Bratec et al., 2015). The phase between the two sine functions was shifted by 96° so that each CS predicted US occurrence with a different probability at each time point. Participants were told that the two symbols (whose assignment to a particular CS-US contingency was counterbalanced across participants) predicted US occurence with different probabilities, and that they should keep in mind that these probabilities could change throughout the run. With this in mind, they were asked to predict the occurrence of a US after a particular CS, with the CS-US contingency systematically fluctuating throughout the experiment, forcing participants to constantly adapt their predictions. All participants complied with experimental instructions.

Behavioral Measures

Learning performance scores were calculated as subject-specific correlations between predicted and actual outcomes across trials for each condition. Emotional intensity ratings, in contrast, were feeling scores gathered at the end of each trial. The two behavioral measures were subjected to paired t-tests, comparing Alone and Social conditions. More importantly, the two measures were used for testing associations between brain- and behavior-related changes induced by a social context change.

Computational Model

Aversive predictions (aPs) and aPEs were computed based on the Rescorla Wagner (RW) rule (Rescorla & Wagner, 1972). For a trial *t*, aPE was calculated as a difference between the actual outcome *R(t)* and the predicted outcome *aP(t)*:

$$aPE(t) = R(T) - aP(t) \times U(t)$$

In turn, predicted outcome for the next trial *aP*(*t+1),* was updated by adding aPE of the current trial *aPE(t)* to *aP(t)*, weighted by a learning rate λ:

$$aP(t+1) = aP(t) + \lambda aPE(t) \times U(t+1)$$

Parameter R was set to 1 when the aversive picture was delivered, and to 0 when no picture was shown. In turn, parameter *U* was used to disentangle CS1 and CS2 trials. Specifically, to calculate aP and aPE values related to CS1, *U* was set to 1 on CS1 trials, and to 0 on CS2 trials, and vice versa for the calculation of aPs and aPEs related to CS2 (Mulej Bratec et al., 2015).

We used a low λ of 0.05, due to the similarity of design and to be able to meaningfully compare results of this study with a recent study investigating the effects of cognitive emotion regulation on aversive stimulus- and prediction error-related activity in the brain, including AI (Mulej Bratec et al., 2015).

MRI Acquisition

Measurements were performed on a 3T Siemens scanner at the Klinikum rechts der Isar, Technische Universitaet Muenchen. Visual stimuli, presented with Presentation software (Neurobehavioral Systems), were rear-projected on a screen at scanner head and were visible via an adjustable mirror mounted to a standard head coil. Presentation software also received trigger pulses from the scanner.

Anatomical images were acquired with the magnetization-prepared rapid acquisition gradient echo (MP-RAGE) T1-weighted sequence (1 × 1 × 1 mm resolution), and functional scans with the contrast-gradient echo-planar T2*-weighted sequence with a repetition time of 2 s, echo time of 30 ms, flip angle of 90°, acquisition matrix of 64 × 64, 35 slices, each 3 mm thick, with a gap of 0.6 mm, and an in-plane resolution of 3 × 3 mm.

fMRI Data Analysis

All analyses were carried out with SPM8 (Wellcome Department of Cognitive Neurology, London, UK). The T2*-weighted functional images were slice-timed, then realigned to the first image of the first run (after discarding the first two volumes) and unwarped. T1-weighted structural images were coregistered to the functional images, segmented and then normalized to a standard T1 template in the Montreal Neurological Institute (MNI) space with a 1 × 1 × 1 mm resolution. Normalization

parameters from the latter were used to normalize the functional images, which were then resampled to 3 × 3 × 3 mm, smoothed with an 8 mm full-width-at-half-maximum Gaussian filter, and temporally high-pass filtered with a cut-off of 128 s. General linear model (GLM)-based statistical analysis with the following regressors was performed: a) hemodynamic response function (HRF)-convolved onsets of CS1, CS2, US-Paired, US-nonPaired, Regulation Instructions, and Valence Scale; b) aP and aPE values derived from the RW rule as parametric modulations (PM) of the onset regressors: aP1 and aP2 as PM of CS1 and CS2 onsets, respectively, plus aPE-Paired and aPE-nonPaired as PM of US-Paired and US-nonPaired onsets, respectively; and c) 6 movement regressors derived from realignment as regressors of no interest. Analysis of the current study focused on Paired trials only, (Mulej Bratec et al., 2015).

Based on the hypothesis that a change in the social context would affect different types of activity in insula subregions during aversive conditioning, a ROI-based analysis focused on AI and PI was carried out. The two right insula ROIs were spheres centered on coordinates from previous studies, with a radius of 8 mm. The right AI ROI central coordinate (x = 40, y = 24, z = -8) was taken from a study on aversive PE-related activity in the AI (Pessiglione et al., 2006), while the PI ROI coordinate (x = 45, y = -20, z = 16) was taken from a study in which PI stimulus-related activity was suppressed by social context in the context of aversive emotional processing (Younger et al., 2010). The two left insula ROIs were spheres with a radius of 8 mm, reflecting right AI and PI coordinates. The left AI ROI central coordinate (x = -40, y = 24, z = -8) was a left-sided 'mirror' coordinate of the right AI coordinate. The left PI ROI central coordinate (x = -41, y = -20, z = 16) was similarly a 'mirror' coordinate of the right PI ROI, taken from the same study as the right PI ROI (Younger et al., 2010).

With regard to social context effects on the two types of brain activity, a similar pattern of results was expected for the right and left insula. We thus completed the analyses for right and left insulae consecutively. For both AI and PI ROIs of one side, the two dependent variables were prediction error- and aversive stimulus-related blood-oxygen-level dependent (BOLD) activity, while the two factors were Social

Context (Alone, Social) and Insula Subregion (AI, PI). Average ß-values for both prediction error- and aversive stimulus-related activity were extracted from the ROIs and subjected to a 2x2 multivariate analysis of variance (MANOVA). The left insula MANOVA was based on 17 participants, after removing an outlier (> 2.5 standard deviations for prediction error-related activity).

To explore the relationship of the above effect with the social context effect on learning performance and feelings, the extracted ß-values from the right and left insula ROIs were additionally subjected to correlations with behavioral scores (i.e., learning performance and emotional intensity ratings).

Results

Social Context Affects Distinct Types of Activity in the AI and PI Subregions of the Right and Left Insula

Motivated by the hypothesis that a change in the social context would affect different types of activity in the right and left insula subregions, we carried out two 2x2 MANOVAs, with two dependent variables –aversive stimulus- and prediction error-related BOLD activity. Focusing on aversive stimulus-related activity in the right insula, MANOVA revealed a significant main effect of Social Context (F = 8.07, p = 0.011) and Insula Subregion (F = 14.21, p = 0.002). Crucially, there was a significant interaction between the two factors (F = 8.10, p = 0.011), such that aversive stimulus-related activity was differentially affected by social context in the right AI and PI. Planned t-tests revealed that the presence of a psychotherapist affected aversive stimulus-related activity only in the right PI (t = -3.33, p = 0.002) but not in the right AI (t = 0.06, p = 0.475), as expected (Figure 1A *left*).

Results for the left insula were analogous to those of the right insula. Concentrating on aversive stimulus-related activity, the left insula-focused MANOVA revealed a significant main effect of Social Context (F = 12.10, p = 0.003) and Insula Subregion (F = 16.72, p = 0.001). Crucially, there was a significant interaction between the two factors (F = 9.87, p = 0.006), such that aversive stimulus-related BOLD activity was differentially affected by social context in the left AI and PI. Planned t-tests revealed that the presence of a psychotherapist affected aversive stimulus-related activity

only in the left PI (t = -4.07, p = 0.0004) but not in the left AI (t = -0.07, p = 0.472), as expected (Figure 1B *left*).

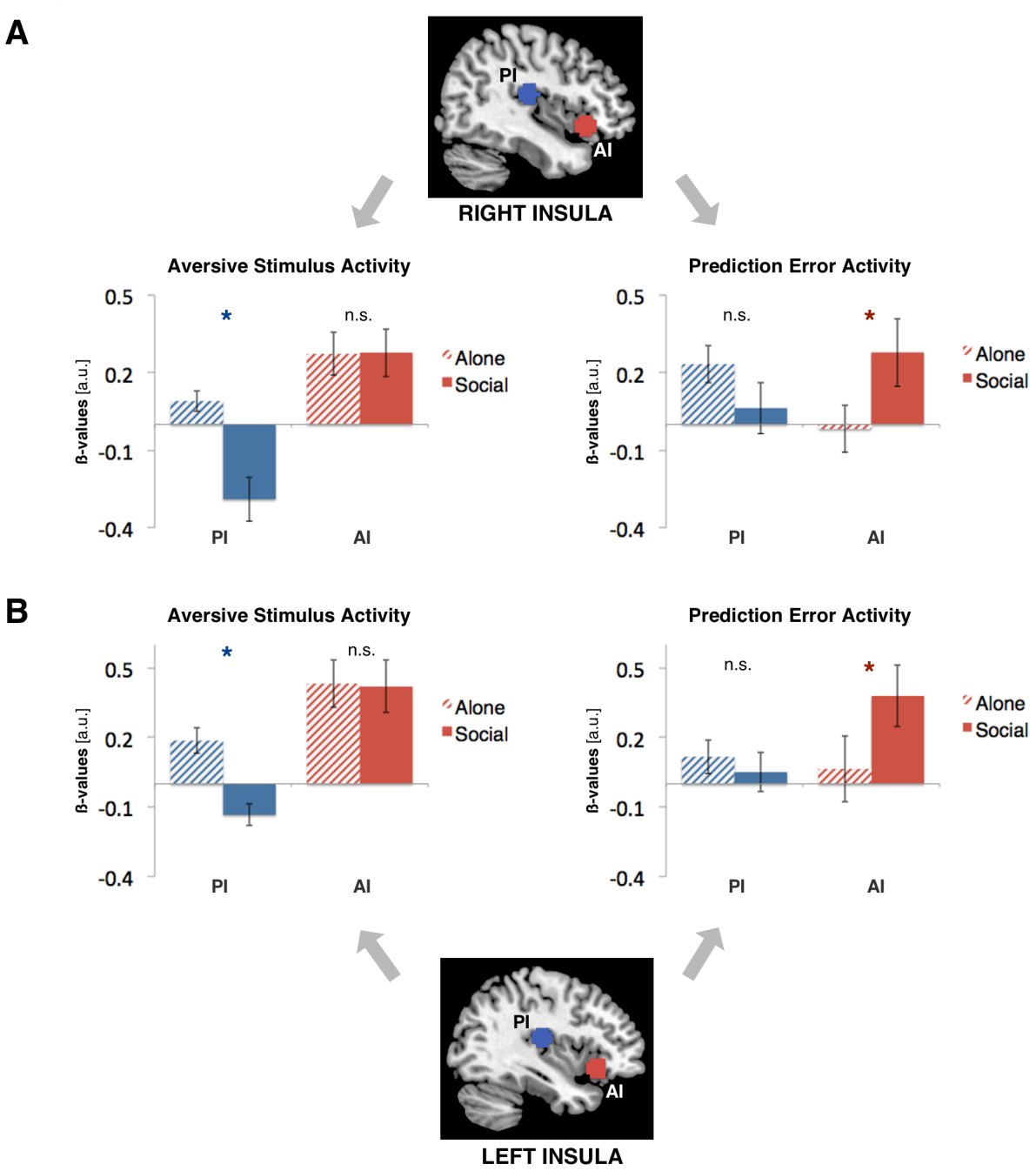

Figure 1. The effect of social context on the right and left AI and PI activity. (A) Social Context × Insula Subregion interaction pattern for the aversive stimulus-related activity (*left*) and the aversive prediction error-related activity (*right*) of the right insula. (B) Social Context × Insula Subregion interaction pattern for the aversive stimulus-related activity (*left*) and the aversive prediction error-related activity (*right*) of the left insula. * p < 0.05; n.s. – non-significant.

Focusing on aversive prediction error-related activity in the right insula, the MANOVA revealed a significant interaction between the two factors Social Context and Insula Subregion ($F = 4.91$, $p = 0.041$), such that prediction error-related BOLD activity was differentially affected by social context in the AI and PI. Planned t-tests revealed that the presence of a psychotherapist affected prediction error-related activity only in the AI ($t = 2.25$, $p = 0.019$) but not in the PI ($t = -1.18$, $p = 0.128$), as hypothesized (Figure 1A *right*).

The result was consistent in the left insula. Concentrating on aversive prediction error-related activity, the left insula-focused MANOVA revealed a trend for a significant interaction between the two factors Social Context and Insula Subregion ($F = 4.14$, $p = 0.059$). Planned t-tests revealed that the presence of a psychotherapist affected prediction error-related activity only in the AI ($t = 2.01$, $p = 0.031$) but not in the PI ($t = -0.71$, $p = 0.244$), as hypothesized (Figure 1B *right*).

Altogether, results confirm that a change in the social context from Alone to Social reduced only stimulus-related activity in the left and right PI, while enhancing only aversive prediction error-related activity in the left and right AI.

Enhanced Activity in the Right and Left AI Distinctively Relates to Social Context-Induced Changes in Behavioral Learning Performance

Paired t-tests revealed that a change in the social context did not significantly influence emotional intensity ($t = 1.12$, $p = 0.279$) or learning performance scores ($t = -1.21$, $p = 0.245$). Following our hypothesis that the expected increase of AI activity in the right and left AI might be differentially associated with social context-induced changes in the behavioral learning performance scores, we correlated aversive prediction error-related fluctuations due to the social context change in the right and left AI, respectively, with changes in behavioral learning performance due to social context. First examining the right AI, correlation analysis revealed that the increase of prediction error-related activity in the right AI was positively correlated with the change in learning performance during the social compared to the alone run ($r = 0.42$, $p = 0.043$) (Figure 2A *center*). In other words, the stronger the

increase of prediction-error activity in the right AI, the higher the learning performance during the social, compared to the alone, session.

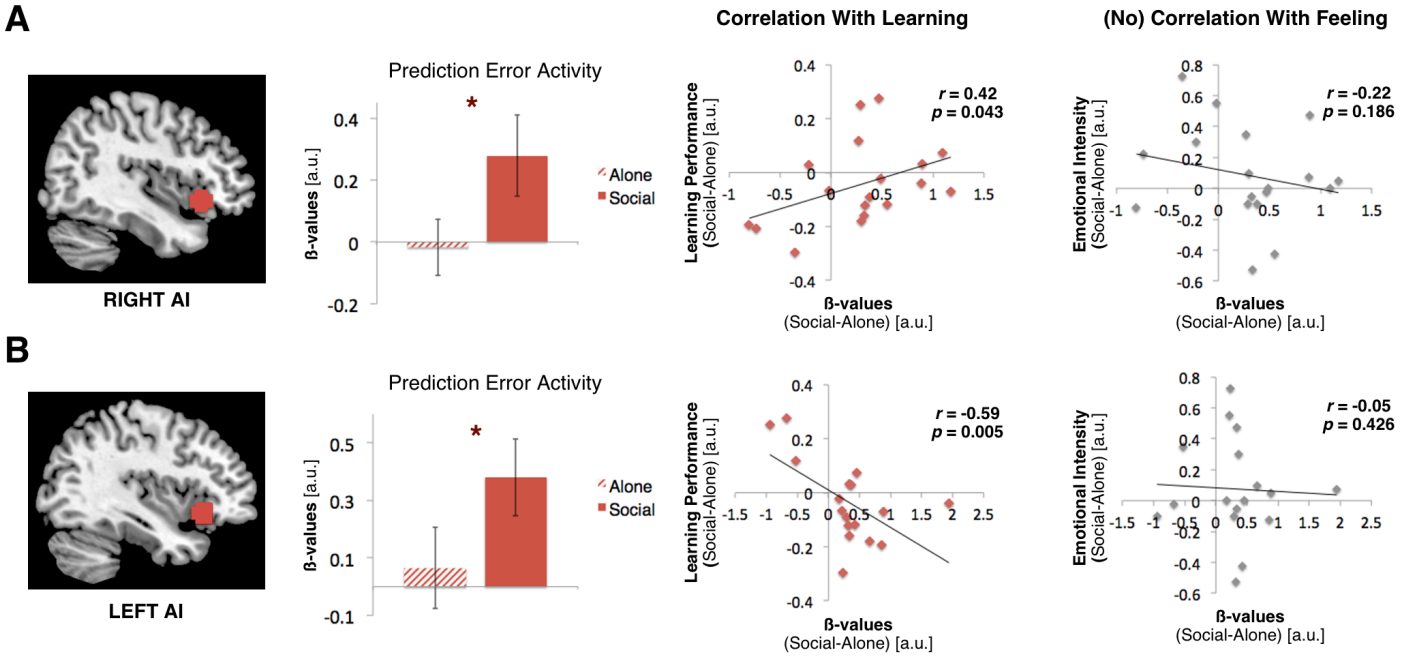

Figure 2. Brain-behavior correlations for right and left AI. (A) The effect of social context on the prediction error-related activity in the right AI (*left*) was positively correlated with learning performance change during the social run, compared to the alone run (*center*), but did not correlate with emotional intensity ratings (*right*). (B) The effect of social context on the prediction error-related activity in the left AI (*left*) was negatively correlated with learning performance change during the social run, compared to the alone run (*center*), but did not correlate with emotional intensity ratings (*right*). * $p < 0.05$; n.s. – non-significant; AI – anterior insula.

Focusing on the left AI, correlation analysis revealed that the increase of prediction error-related activity in the left AI was negatively correlated with the change in learning performance during the social run (r = -0.59, p = 0.005; Figure 2B *center*), showing an opposite correlation to that of the right-sided AI (Figure 2A *center*). In other words, while the stronger activity in the right AI was related to a relatively higher aversive learning-related performance, the stronger activity in the left AI was related to a relatively lower aversive learning-related performance during the social session, in contrast to the alone session.

To test whether correlations with AI prediction error-related activity fluctuations were specific to learning performance scores, a similar correlation analysis was

carried out on emotional intensity ratings. The correlation analysis relating changes in AI prediction error-related activity with emotional intensity fluctuations due to social context change revealed no significant correlations for either the right AI (r = -0.22, p = 0.186; Figure 2A *right*) or the left AI (r = -0.05, p = 0.426; Figure 2B *right*).

To further specify whether social context-induced activity fluctuations in the right and left AI were indeed specifically differentially correlated with behavioral learning performance changes and were not directly negatively related to each other, we correlated the prediction error-related activity fluctuations due to social context change of the right AI with that of the left AI. The correlation was not significant, r = 0.17, p = 0.257), showing that social context-induced activity increases in the right and left AI were not related to each other.

Altogether, results confirm a differential association between activity changes in the right and left AI and behavioral learning performance fluctuations due to social context change. The stronger the prediction error-related activity in the right AI during the social session, compared to the alone session, the relatively higher the learning performance during the social in contrast to the alone run. In contrast, the stronger the social context-induced prediction error-related activity in the left AI, the lower the learning performance during the social, compared to the alone, session.

Discussion

The current study investigated neural mechanisms supporting socio-emotional processing in the insula subregions by way of manipulating social context during aversive conditioning. More specifically, the study focused on the question of whether a change in the social context from 'alone' to 'social' would affect AI and PI differently, by targeting distinct types of aversive emotional activity in the two regions, and the right and left AI differently, in line with their differential involvement in aversive and positive emotions, respectively. Results point to a three-fold dissociation between brain signal types, insula sub-regions, and right and left AI. 1) In both right and left insula sub-parts, prediction error-related activity was affected by the social context in the AI but not the PI, while aversive stimulus-

related activity was changed by the social context in the PI but not the AI (Figure 1). The finding highlights a double dissociation between signal types and insula subregions (Craig, 2009; Gu et al., 2013; Lamm & Singer, 2010; Seth, 2013). 2) The change in learning performance due to social context was differentially correlated with the right and left AI prediction error-related activity increase during the social session, compared to the alone session (Figure 2). The higher the social context-induced enhancement of right AI prediction error-related activity, the better the learning performance during the social, in comparison to the alone run. In contrast, the more left AI prediction error-related activity increased during the social run, the worse the social learning performance. The finding illuminates the negative-positive affect dissociation between right and left AI, respectively (Craig, 2009; 2005; 2010). In summary, manipulating the social context, the current study was able to reveal differences in the underlying mechanisms of posterior and anterior, as well as right and left insula subregions.

Social Context Specifically Affects Aversive Stimulus-Related Activity in the PI and Aversive Prediction Error-Related Activity in the AI

A change in the social context from 'alone' to 'social' affected aversive stimulus-related activity in the bilateral PI but not AI (Figures 1A *left* & 1B *left,* for right and left insula, respectively), while modulating aversive prediction error-related activity in the AI but not the PI (Figures 1A *right* & 1B *right,* for right and left insula, respectively), as hypothesized. Results support and extend previous work on the posterior-to-anterior gradient in the insula, which posits that posterior parts of the insula mostly support primary representations of interoceptive states associated with experiencing salient events, such as pain or risk (Singer et al., 2006, 2009; Xue et al., 2010), while anterior parts support higher-order integrated representations of feelings, also expressed as aversive prediction errors (Craig, 2009; Gu et al., 2013; Lamm & Singer, 2010; Seth, 2013).

Correspondingly, current results show that a change in the social context specifically affected aversive stimulus-related activity in the bilateral PI (Figures 1A *left* & 1B *left,* for right and left insula, respectively). Based on the general linear model, stimulus-related activity reflected a consistent activation in the region every

time a negative picture was presented, and thus likely represents activity related to primary representations of interoceptive states and negative feelings associated with the shown aversive pictures, in line with previous accounts of functional specialization of the PI (Bauernfeind et al., 2013; Craig, 2009; 2003; 2010; Menon & Uddin, 2010).

In further correspondence with the posterior-to-anterior insula gradient, social context change in the current study specifically affected aversive prediction error-related activity in the (ventral) AI (Figures 1A *right* & 1B *right,* for right and left insula, respectively). In contrast to the stimulus-related activity, based on the general linear model, prediction error-related activity represents a parametric modulation of the aversive stimulus onset, and thus reflects activity related to the mismatch between a prior expectation of seeing an aversive picture on the next trial and the reality of such a picture being present or absent on the said trial (Mulej Bratec et al., 2015; Ouden et al., 2012; Schultz & Dickinson, 2000). The association of AI with aversive prediction error-related activity confirms previous accounts of aversive prediction error encoding within the (ventral) AI in the context of associative learning (Garrison et al., 2013; Kim et al., 2006; Pessiglione et al., 2006; Seymour et al., 2004).

The current findings can also be considered from the predictive coding account (Clark, 2013; Friston, 2005; 2009). Predictive coding models see prediction error-based processing as the universal computation of the layered cortex, such that the cortex is viewed as organized in a hierarchical fashion, with every level (or brain region) containing two types of units – prediction error units and representation units (Clark, 2013; Friston, 2005; 2009). The representation units provide predictions, based on a complex model of the world, to hierarchically lower areas, thus representing feedback signals. The latter are compared with the feed-forward signals (i.e., prediction error signals from the preceding level) by the prediction error units at every level (Clark, 2013; Friston, 2005; 2009). The predictive coding account thus proposes that two types of activity – prediction error- and stimulus representation-related activity – should be present in every region of the brain, including different parts of the insula. In this framework, results of our study

suggest that social context specifically targets prediction error 'units' in the AI, while selectively affecting the representation 'units' in the PI. Further studies could help investigate the existence and functional properties of prediction error and representation 'units' in the insula subregions.

The Social Context Effects on Insular Activity Resemble those of Cognitive Emotion Regulation

A change in the social context did not only affect different types of brain activity in the bilateral AI and PI, but in fact modulated the two activity types in opposite ways. The shift from 'alone' to 'social' in the current study, or in other words from being by yourself to being in the presence of a trustworthy but newly acquainted individual, *suppressed* aversive stimulus-related activity in the PI, but *enhanced* aversive prediction error-related activity in the AI (Figure 1). It is interesting to note that the effects of social presence seem to resemble those of self-administered cognitive emotion regulation. In a recent study, cognitive emotion regulation enhanced aversive prediction error activity in a range of areas, including the ventral insula, but suppressed aversive stimulus-related activity in an extended emotional brain network, including the posterior dorsal insular cortex (Mulej Bratec et al., 2015).

The correspondence between simple social presence effects and the impact of cognitive emotion regulation in the insula is striking, especially considering that the social session in the current study resembled a 'no regulation' or 'attend' condition of a typical emotion regulation experiment, including the above-mentioned study (Mulej Bratec et al., 2015). It implies that a supportive presence of a trustworthy individual, even if previously unknown, can have a powerful effect on the insula activity, resembling that of cognitive emotion regulation, a highly effective strategy of emotion control (Ochsner, Silvers, & Buhle, 2012). This is in line with the social baseline theory, which posits that social proximity of trusting others reduces threatening feelings, resembling cognitive affect regulation without the additional use of cognitive control systems (Beckes & Coan, 2011; Coan & Sbarra, 2015). Moreover, a change in the social context further modulated prediction error-related activity in the AI due to changed primary representations of interoceptive states in

response to aversive stimuli, as indexed by the PI activity fluctuations. This is in good agreement with the posterior-to-anterior insula gradient account, which underlines the importance of AI in integrating PI's representations of sensations and homeostatic states to salient stimuli into higher-order cognitive processes, such as aversive conditioning (Bauernfeind et al., 2013; Menon & Uddin, 2010).

Differential Relationships Between AI Activity Increase and Behavioral Learning Performance Change Point to Right-Left AI Differences.

Results show that prediction error-related activity was consistently increased by the social context change in both right and left AI (Figures 2A *left* & 2B *left* for right and left insula, respectively). To examine potential hemispheric differences, supported by the differential involvement or right and left insula sub-parts in aversive and positive emotions, respectively, the increase of right AI activity was correlated with the subject-specific learning performance changes induced by the social context. The increase of prediction error-related activity in the right AI was associated with an *increase* in learning performance during the social, compared to the alone, session (Figure 2A *center*), while the increase of prediction error-related activity in the left AI was associated with a *decrease* in learning performance during the social session, in contrast to the alone one (Figure 2B *center*). The association between AI prediction error-related activity and learning performance was specific, as corresponding associations with changes in emotional rating scores were not significant (Figure 2).

Results are well aligned with Craig's account of left-right AI asymmetry, which states that left and right AI are typically co-activated yet seem to be involved in positive and negative affect and in the control of the parasympathetic and sympathetic autonomous system, respectively (Craig, 2009; 2005; 2010). Correspondingly, current results demonstrate that on average, both left and right AI prediction error-related activity was increased with social context change, but that the level of increase was associated with an increased aversive learning performance in the right AI and a decreased learning of aversive associations in the left AI, in line with both negative-positive affect and sympathetic-parasympathetic control asymmetry for right and left AI, respectively. We additionally tested

whether the social context-related increases of both right and left AI aversive prediction error-related activations were related to each other via correlation analysis and did not find a significant association. The result indicates that the social impact on AI prediction error-related activity increase is independent for left and right AI. Assuming that the increase of prediction error-related AI activity is relevant for controlling the autonomous nervous system, the result suggests that social context influences such control of the parasympathetic and sympathetic nervous systems independently, with independent effects on learning performance.

Conclusion

Drawing on the posterior-to-anterior insula gradient account, the current study was able to demonstrate a three-fold dissociation between AI and PI, left and right AI, and two distinct brain activity types, induced by the social context. While the aversive stimulus-related activity was affected by the change from 'alone' to 'social' only in the PI, the prediction error-related activity was affected only in the AI; furthermore, the AI activity increase was differentially associated with behavioral learning performance scores for the right and left AI parts. The study provides new insights into how the presence of a trustworthy other can affect distinct types of emotional activity in insula subregions, while also contributing a novel paradigm to study the effects of social context on emotional brain activity.

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6

General Discussion: An Extended Account of Emotion Regulation

The current thesis aimed to extend the concept of emotion regulation by re-evaluating both the *emotion* and the *regulation* parts of the concept as it is conventionally viewed. To achieve this aim, four projects were conducted, the first two focused on the *emotion,* and the second two centred on the *regulation* part of emotion regulation. The General Discussion section provides an overview of the studies, their findings and conclusions that can be drawn from them. The first part of the section summarises main findings and relates them to the current state of the literature, separately touching on the extension of *emotion* and the extension of *regulation* in the context of emotion regulation. To provide a comprehensive account of the findings and how they relate to each other, the second part of the section provides an additional analysis of similarities and differences in the relevant effects across projects. The third part of the General Discussion section includes a critical analysis of important methodological issues, while the fourth part offers suggestions for future research. The section finishes with a conclusion.

6.1 Key Findings and Their Implications for Emotion Regulation

To address the aims of the current thesis, four separate projects were conducted, resulting in four original research manuscripts: 1) Cognitive emotion regulation enhances aversive prediction error activity while reducing emotional responses (Mulej Bratec et al., 2015); 2) Cognitive emotion regulation modulates the balance of competing influences on ventral striatal aversive prediction error signals (unpublished); 3) How do you make me feel better? Social cognitive emotion regulation and the default mode network (Xie, Mulej Bratec et al., 2016); and 4) Social context affects distinct types of emotional activity in subregions of the human insula (unpublished). While projects 1 and 2 extend the *emotion* part of emotion regulation, projects 3 and 4 expand the *regulation* part. The current section includes

a summary of key findings and how they relate to the current state of the field. The first part of the section focuses on main results of projects 1 and 2, while the second part discusses findings of projects 3 and 4.

6.1.1 Extending the Emotion Part of Emotion Regulation

In the context of emotion regulation, emotions are primarily seen as responses to stimuli in the environment (Ochsner et al., 2012). However, it is important to consider that emotions have other important roles, including that of motivating our actions (Izard, 2009; Lang & Bradley, 2010). With the aim of incorporating the motivating aspect of emotions into the theory of emotion regulation (see section *1.2 Emotion, Motivation and Prediction Errors*), projects 1 and 2 of the current thesis examined whether emotion regulation modulates not only emotional responses, but also affects the brain signal for motivated behaviour – the prediction error signal.

Project 1 (Mulej Bratec et al., 2015) set out to directly compare the influence of cognitive emotion regulation on aversive prediction error-related, in contrast to aversive response-related, activity across the whole brain. In the study, participants employed a reappraisal strategy of self-distancing while being exposed to an aversive Pavlovian learning paradigm involving highly arousing and aversive pictures as unconditioned stimuli. This was contrasted with the condition in which participants simply paid attention to the stimuli, without trying to change their emotions in any way.

Results demonstrated, firstly, that emotion regulation indeed reduced subjective emotional feelings, as well as emotional response-related brain activity in a wide network of brain regions, including the insula, hippocampus, ventral tegmental area and periaqueductal gray. The higher the regulation success (i.e., suppression of negative feelings), the stronger the reduction of aversive response-related activity, indicating the relevance of the latter effect for emotion regulation. Secondly, and most importantly, the study showed that emotion regulation also affected aversive prediction error-related activity, such that this activity was enhanced in the ventral tegmental area, ventral striatum, ventral insula and hippocampus. The worse the participants' learning performance during reappraisal, the stronger the

enhancement of aversive prediction error activity, suggesting a meaningful relationship between the behavioural and the neural effects of reappraisal on motivational learning. Interestingly, the effects of emotion regulation on aversive response- and aversive prediction error-related activity overlapped in the ventral tegmental area, insula and hippocampus, implying a shared regulatory source. Last but not least, a ventral PFC cluster, one of three involved in regulation in this study, increased its connectivity with the ventral tegmental area during reappraisal, with the effect being related to the learning performance change during regulation.

All-in-all, project 1 of this thesis extends the *emotion* concept of emotion regulation, by showing that emotion regulation influences not only emotional responses, but also the brain signal related to the motivational aspect of emotions – the prediction error signal. The effect of reappraisal on prediction error-related activity was centred on the ventral tegmental area, also considered the source of prediction error signals (Bromberg-Martin, Matsumoto, & Hikosaka, 2010; Matsumoto & Hikosaka, 2009), ventral striatum, ventral insula and hippocampus.

Project 2's (unpublished) aim was to determine whether cognitive emotion regulation targets the network of motivated behaviour by targeting prediction error-related input to the ventral striatum. As such, the aim of project 2 was similar to that of project 1, i.e., to test whether emotion regulation also affects the motivational aspect of emotions. However, the research question was approached from a different angle. In brief, we took an established model of motivated behaviour, based on animal studies, and used it to test whether reappraisal, a type of cognitive emotion regulation, affects the influence of ventral striatal afferents on ventral striatal prediction error-related activity. In animal models of motivated behaviour, ventral striatum is seen as the integration centre, receiving and integrating information from various, often competing, sources (i.e., PFC, hippocampus, amygdala and ventral tegmental area) (Grace et al., 2007; Pennartz et al., 2009; 2011; Sesack & Grace, 2010).

Combining model-based fMRI and psychophysiological interaction analysis, the study was able to demonstrate that reappraisal indeed affects the influence of

striatal afferents on the ventral striatal prediction error signals. Even more, the effect was related to participants' reappraisal ability. In superior regulators, the relative influence of PFC on ventral striatal prediction error activity was increased, while the impact of subcortical afferents (i.e., ventral striatum, ventral tegmental area and hippocampus) was reduced. In contrast, inferior regulators failed to suppress the subcortical influence and instead showed a reduced impact of the PFC.

Altogether, project 2 extends the *emotion* part of emotion regulation by showing that cognitive emotion regulation directly targets the network of motivated behaviour centred on the ventral striatum and its inputs, representing the motivational aspect of emotions. Furthermore, project 2 highlights the importance of inter-individual differences in reappraisal ability for the regulation of ventral striatum and the associated network of motivated behaviour.

6.1.2 Extending the Regulation Part of Emotion Regulation

It is often underemphasized or even overlooked that our emotions are not only regulated by ourselves, but are also influenced, intentionally and unintentionally, by others around us (Reeck et al., 2015). As a result, social emotion regulation and its neural underpinnings remain largely unexplored, despite the known importance of social emotion regulation for both the general well being (Clark et al., 1998; Reeck et al., 2015) and the treatment of affective disorders characterised by impaired emotion regulation, such as major depression and anxiety (Cuijpers et al., 2013; DeRubeis, Siegle, & Hollon, 2008; Frewen, Dozois, & Lanius, 2010). Projects 3 and 4 of this thesis focused on the effects and the neural underpinnings of social emotion regulation and modulation, respectively, thus extending the *regulation* part of emotion regulation to include not only intrapersonal, but also interpersonal, i.e., social emotion regulation.

Project 3 of the current thesis (Xie, Mulej Bratec et al., 2016) aimed to explore the neural underpinnings of social cognitive emotion regulation by way of social reappraisal. Participants met a psychotherapist at their arrival and were told that she could communicate with them 'online' throughout the experiment, in which they were exposed to highly aversive pictures. In reality, pre-recorded videos were

used at the beginning of each trial. In half of the trials, the therapist used reappraisal to regulate participants' emotions; in the other half, she simply told them to attend to the pictures, resembling an 'attend' or no regulation condition of a typical emotion regulation experiment.

The study showed that social cognitive emotion regulation was successful at lowering participants' negative feelings. Most importantly, social reappraisal recruited dorsolateral and dorsomedial PFC, orbitofrontal cortex, anterior cingulate, inferior parietal cortex, and precuneus, largely overlapping with the default mode network, whose areas are known to be involved in both cognitive emotion regulation and social cognitive processes (Lindquist et al., 2012; Schilbach et al., 2012). Confirming that the activations were indeed related to the social regulation of emotion, activity increases in the left inferior parietal cortex and precuneus correlated with social regulation success (i.e., the difference in feeling scores between the social regulation and no regulation conditions). In contrast, emotion-related activity was suppressed by social regulation in the bilateral supramarginal gyrus, temporal and occipital cortices, and the left insula, consistent with previous emotion regulation studies (Kanske et al., 2011; McRae et al., 2010). Results of the study further showed that social reappraisal was related to individual characteristics of social functioning, such that individual attachment security scores were related to both social regulation success and the involvement of OFC in social reappraisal. Attachment security has previously been associated with changes in pain ratings and the associated neural activity during social support (Hurter, Paloyelis, Williams, & Fotopoulou, 2014; Krahé et al., 2015; Sambo, Howard, Kopelman, Williams, & Fotopoulou, 2010).

The study involved two additional analyses to further specify the neural network supporting social reappraisal. Firstly, there was a high (around 60 %) overlap between the social reappraisal network and the default mode network identified from resting-state data of the same participants. The overlap confirmed that social reappraisal indeed largely involved the default mode network. Secondly, social reappraisal was contrasted with intrapersonal reappraisal. The self-social reappraisal network overlap demonstrated that both types of emotion regulation

recruited a cognitive control network, including dorsolateral and medial PFC and the inferior parietal cortex. Crucially, social reappraisal-specific brain regions (in contrast to intrapersonal reappraisal) spanned dorsomedial PFC, precuneus and left TPJ, all of which belong to the so-called 'social default mode network', i.e., a default mode network sub-network involved in social cognitive processes (Schilbach et al., 2012).

In summary, project 3 extends the *regulation* part of emotion regulation by delineating the neural underpinnings of social cognitive emotion regulation, particularly social reappraisal. The project shows that social cognitive emotion regulation recruits the default mode network, whose regions are involved in both cognitive emotion regulation and social cognitive processes (Lindquist et al., 2012; Schilbach et al., 2012). It further demonstrates the relevance of individual differences in attachment security for social reappraisal effectiveness.

Project 4 (unpublished) set out to determine the impact of social emotion modulation on aversive conditioning in the insula, to better delineate the role of insula and its subregions in social-emotional behaviour. In detail, we investigated the influence of a social context change (i.e., from 'alone' to 'social') on insular activity with regard to 3 dimensions: aversive stimulus – prediction error-related activity (distinct types of activity, both relevant for emotional behaviour (Mulej Bratec et al., 2015; Ouden et al., 2012)), anterior – posterior insula (due to the proposed posterior-to-anterior functional gradient in the insula (Craig, 2009; Gu, Hof, Friston, & Fan, 2013; Lamm & Singer, 2010; Seth, 2013)), and right – left insula (due to their control of sympathetic and parasympathetic nervous systems, respectively (Craig, 2009; 2005; 2010)). Participants were exposed to aversive Pavlovian conditioning, with highly negative pictures serving as unconditioned stimuli. A psychotherapist, whom they had met in person before scanning, accompanied them in half of the experiment (seemingly live via a camera-microphone system; in reality, videos were used); in the other half, they completed the task while being alone. Both self and social sessions resembled a no-regulation condition of a typical emotion regulation experiment, with participants or the

psychotherapist (depending on the condition) not trying to change participants' emotions.

Results demonstrated that the presence of a trustworthy person supressed aversive stimulus-related activity in the posterior, but not the anterior, insula. In contrast, aversive prediction error-related activity was enhanced in the anterior, but not the posterior, insula. The differential effect of social context on activity types in the two insula subregions reinforces the view of a posterior-to-anterior functional gradient in the insula, which suggests that functional complexity increases from posterior to anterior insula parts (Craig, 2009; Gu et al., 2013; Lamm & Singer, 2010; Seth, 2013). Furthermore, the study showed that the effect of social context was positively correlated with behavioural aversive learning performance in the right insula, but negatively correlated with the same performance in the left insula. This second finding is in line with the differential control of sympathetic and parasympathetic nervous systems by the right and left insula, respectively (Craig, 2009; 2005; 2010).

Altogether, project 4 extends the *regulation* part of emotion regulation by exploring the effects of social emotion modulation on distinct types of neural activity in different insula subregions. Importantly, the project also takes the motivational aspect of emotions into account by analysing prediction error-related activity in the insula, thus additionally touching on and expanding the *emotion* part of emotion regulation. As such, the last project of the current thesis represents a study that fully incorporates the extended account of emotion regulation, considering emotions to be more than responses to stimuli, as well as incorporating the so-far under-investigated social modulation of emotion.

6.2 Analysis of Relevant Effects Across Projects

As a whole, projects of the current thesis expand the concept of emotion regulation. To that end, each project focused on a specific emotion regulation type and examined its effect on relevant brain activity and/or connectivity. The projects thus covered three types of emotion regulation: intrapersonal reappraisal (projects 1

and 2), social reappraisal (project 3) and social emotion modulation (project 4), and focused on specific research questions (see section *6.1 Key Findings and their Implications for Emotion Regulation*). The current section discusses noteworthy similarities and differences in emotion regulation effects across projects. The first part of the section examines effects of different regulation types on aversive stimulus-related activity in the posterior insula (drawing on projects 1, 3 and 4), while the second part focuses on the effects of intrapersonal reappraisal and social emotion modulation on prediction error-related activity in the anterior insula (drawing on projects 1 and 4).

6.2.1 Reduction of Stimulus Activity Across Regulation Types in the Posterior Insula

A closer examination of results from projects 1, 3 and 4 reveals that aversive stimulus-related activity was reduced in the posterior insula in all three projects. Since each project focused on a different type of emotion regulation, this implies that all three types of emotion regulation (i.e., intrapersonal reappraisal, social reappraisal and social emotion modulation) similarly affected emotion-related activity in the posterior insula.

The reduction of aversive stimulus-related activity during intrapersonal reappraisal was centred on bilateral posterior regions of the posterior insula (local maxima at x = -39, y = -22, y = 1 and x = 39, y = -16, y = -2; see Supplementary Material of project 1). Social reappraisal reduced stimulus-related activity in the left anterior part of the posterior insula (at x = -39, y = -1, y = 1; see Supplementary Material of project 3). Finally, during social emotion modulation, aversive stimulus-related activity was suppressed in bilateral posterior parts of the posterior insula (region of interest analysis for spheres centred around x = -41, y = -20, z = 16 and x = 45, y = -20, z = 16; see Methods and Results of project 4). Since project 4 employed a region-of-interest analysis and the coordinates above thus do not reflect the strongest suppression of activity within the posterior insula, an additional whole brain analysis was carried out (thresholded at $p < 0.05$, FWE cluster-corrected, with a height threshold of $p < 0.005$ and an extent threshold of 180 voxels) on the contrast no regulation > regulation for social emotion modulation. It revealed that during social emotion modulation, aversive stimulus-related activity was maximally

reduced in bilateral posterior insula at x = 45, y = -10, z = 1 (i.e., the anterior part of the right posterior insula) and x = -39, y = -22, z = 13 (i.e., the posterior part of the left posterior insula).

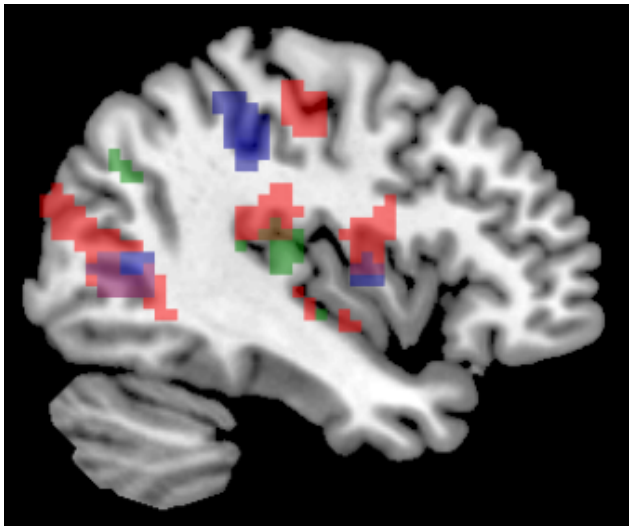

Figure 1: Overlap of the contrast no regulation > regulation for aversive stimulus-related activity during intrapersonal reappraisal (in red), social reappraisal (in blue) and social emotion modulation (in green). The activation maps were thresholded at a height threshold of $p < 0.001$ (uncorrected); x = -41.

To get a better overview of the effects, the three activation maps from the contrast no regulation > regulation for intrapersonal reappraisal, social reappraisal and social emotion modulation were overlapped with each other, each thresholded at a height threshold of $p < 0.001$ (uncorrected). As can be seen in Figure 1, the effects of intrapersonal reappraisal (depicted in red) and social reappraisal (in blue) overlapped in the anterior part of the left posterior insula, while intrapersonal reappraisal (in red) and social emotion modulation (in green) effects overlapped in the posterior region of the left posterior insula. Despite the clear anatomical separation, the affected anterior and posterior subregions of the posterior insula were found to be highly similar in function by a recent meta-analysis: both subregions are a part of the insula that is typically associated with sensorimotor processing, interoception and pain (Kurth, Zilles, Fox, Laird, & Eickhoff, 2010). It is nevertheless interesting to note that social reappraisal and social emotion modulation seem to target different sub-parts of the posterior insula; further studies could help delineate functional differences between the affected insula sub-parts to better explain the disparate effects of social regulation types.

More generally, posterior insula represents interoceptive states and bodily feelings, and also relays these to the anterior insula, which then generates subjective feeling states (Bauernfeind et al., 2013; Craig, 2009; 2003; Kurth et al., 2010; V. Menon & Uddin, 2010). It is thus highly beneficial to target activity in the posterior insula related to the processing of aversive emotional stimuli when trying to regulate emotions. Indeed, the finding that emotional stimulus-related activity was suppressed in the posterior insula by various types of emotion regulation is in line with a variety of previous studies: e.g., those employing intrapersonal reappraisal (Kanske et al., 2011; McRae et al., 2010; Ochsner et al., 2004), intrapersonal distraction (Kanske et al., 2011; McRae et al., 2010), or social emotion modulation (Younger et al., 2010). All-in-all, results of the additional analysis across projects 1, 3 and 4 indicate: 1) that emotional stimulus-related activity in the posterior insula is reduced by emotion regulation across regulation types; and 2) that social reappraisal and social emotion modulation seem to target different parts of the posterior insula, whose potential functional differences, however, are yet to be revealed.

6.2.2 Enhancement of Prediction Error Activity Across Regulation Types in the Anterior Insula

Two projects of the current thesis, projects 1 and 4, looked at effects of emotion regulation on prediction error-related activity. Despite the use of different emotion regulation types (i.e., intrapersonal reappraisal and social emotion modulation, respectively), a similar effect across both projects stands out: 1) both types of emotion regulation enhanced (rather than reduced) prediction error-related brain activity; and 2) both regulation types enhanced prediction error-related activity in the right anterior insula. At the first glance, the focus of effect within the anterior insula appears to differ across intrapersonal reappraisal and social emotion modulation.

Intrapersonal reappraisal enhanced prediction error-related activity in a more posterior ventral part of the right anterior insula (whole-brain analysis, local maximum at x = 42, y = -4, z = -17; see Supplementary Material of project 1). Social emotion modulation, on the other hand, enhanced prediction error-related activity

in a more anterior part of the right anterior insula (region of interest analysis for a sphere centred around x = 40, y = 24, z = -8; see Methods and Results of project 4). To check whether intrapersonal reappraisal and social emotion modulation indeed targeted different subregions of the anterior insula, additional region-of-interest analyses were carried out. Two spherical regions of interest were used, centred on above-presented coordinates from projects 1 and 4, with a radius of 8 mm. Data of project 4 on social emotion modulation were re-analysed first: after extracting β-values from the region of interest defined by results of project 1 (posterior-anterior-insula sphere centre at x = 42, y = -4, z = -17), no significant effect was revealed (t = -0.752, p = 0.463). Data of project 1 on intrapersonal reappraisal were re-analysed next: after extracting β-values from the region of interest defined by project 4 (anterior-anterior-insula sphere centre at x = 40, y = 24, z = -8), I found a significant effect of intrapersonal reappraisal on prediction error-related activity in the anterior part of the anterior insula, equal to that affected by social emotion modulation (t = 2.291, p = 0.034).

Firstly, it is interesting that both types of emotion regulation, albeit very different in nature, enhanced (rather than reduced) prediction-error related brain activity. Owing to the narrow definition of emotion regulation currently in use, very few studies to date have investigated the effects of emotion regulation on prediction error-related activity. One recent study showed that mild stress, which typically invokes automatic emotion regulation (Mauss, Bunge, & Gross, 2007; Phillips et al., 2008), similarly increased aversive prediction error-related activity in the ventral striatum (Robinson et al., 2013). Considering findings of projects 1 and 4 together with those of the above-mentioned study, it seems that an enhancement of prediction error-related activity might be a general effect of emotion regulation, across regulation types. However, further studies, employing a wider range of emotion regulation types and a larger sample could help confirm this hypothesis.

Secondly, both intrapersonal reappraisal and social emotion modulation affected prediction error-related activity in the anterior insula. The anterior insula has previously been associated with prediction errors, including aversive prediction errors (Garrison et al., 2013; Kim, Shimojo, & O'Doherty, 2006; Pessiglione,

Seymour, Flandin, Dolan, & Frith, 2006; Seymour et al., 2004), making it possible for emotion regulation to target this specific type of activity in the region. In a more general sense, anterior insula is thought to support emotional awareness, is known to be involved in complex human emotions, including social emotions, and contains von Economo neurons, which only occur in a few species that have highly developed social skills (Allman et al., 2010; Craig, 2009; Gu et al., 2013; Hogeveen, Bird, Chau, Krueger, & Grafman, 2016; Kelly et al., 2012; Kurth et al., 2010; Lamm & Singer, 2010; Seth, 2013; Singer, Critchley, & Preuschoff, 2009). Therefore, targeting prediction error-related activity in the anterior insula might represent the means by which you could have a profound effect on the person's general emotional state and awareness – in other words, by which you could regulate the person's emotions in a more general sense, without disregarding the motivational aspect of emotions.

Last but not least, it is worth noting that intrapersonal reappraisal and social emotion modulation influenced prediction error-related activity in an overlapping subregion of the anterior insula: the utmost anterior part of the right anterior insula. This is noteworthy considering the processing hierarchy within the insula, which highlights increasing complexity towards anterior insula parts (Craig, 2009; 2011; 2010). In other words, since the very anterior insula integrates various types of information and represents complex emotional and motivational states, targeting this insula subregion maximally enhances the potential impact on emotions and general emotional awareness.

6.3 Methodological Considerations

Considering that the four projects included in this thesis employed novel paradigms or paradigm combinations to examine the effects of various emotion regulation types on different kinds of emotional brain activity (i.e., aversive stimulus- and aversive prediction error-related activity), some methodological issues should be noted. The current section outlines the most relevant methodological considerations and provides further clarification, as well as suggestions for future improvement of paradigms and analyses. It addresses: 1) the choice of a standardized picture set for emotion-evoking stimuli; 2) the employment of Pavlovian conditioning and the Rescorla Wanger model to investigate the

motivational aspect of emotions; and 3) the use of a psychotherapist for the study of social emotion regulation.

6.3.1 Standardised Aversive Emotional Stimuli

All four projects of the current thesis investigated the impact of emotion regulation on aversive emotions and related neural processes, which required that negative emotions be evoked in all participants in a reliable way. To that end, a standardised set of pictures – the International Affective Picture System (IAPS) (Lang, Bradley, & Cuthbert, 2008) – was used in all projects, out of which those pictures with both the highest arousal and most negative valence scores were selected. Such a standardised set of pictures, whose arousal and valence scores have been tested on a large group of subjects and were found stable with regard to both within- and between-subject reliability (Lang et al., 2008), provide a dependable set of stimuli for evoking aversive emotions. They were indeed the stimuli of choice for many existing emotion regulation experiments, as evident from a recent meta-analysis of neuroimaging reappraisal studies (Buhle et al., 2014).

Nevertheless, using participant-specific arousal and valence scores to select appropriate pictures within the set would provide an even surer means of evoking strong emotional responses in the participant group, compared with relying on standardised ratings. Moreover, such participant-specific picture evaluations would allow for additional analyses related to inter-individual differences in emotional responses and emotion regulation. It is also worth noting that aversive emotions can be better evoked by ecologically more valid stimuli, such as videos or participant-specific memories; these are, however, more difficult to control and standardise, potentially weakening group analyses of brain imaging data.

Another alternative to complex emotional materials are painful stimuli, such as mild electric shocks, typically used in Pavlovian learning studies (Gläscher & Büchel, 2005; M. Menon et al., 2007; Seymour et al., 2004; Spoormaker et al., 2011). These reside at the other end of the 'controllability' spectrum: they represent simple and highly dependable aversive stimuli, which do not have to vary in content to consistently evoke an aversive reaction. They may be, however, classified as

'painful' rather than 'emotional' stimuli, thus potentially activating brain networks for both emotion and pain. In addition, reinterpreting the same stimulus again and again by way of reappraisal might prove taxing to the participants, thus lowering emotion regulation effectiveness. All-in-all, choosing emotional stimuli for an emotion regulation experiment is not trivial; the chosen stimuli should satisfy specific research questions in the best possible way, without compromising their reliability to consistently elicit emotional responses in all participants.

6.3.2 Pavlovian Learning and the Rescorla Wagner Model

To extend the *emotion* part of emotion regulation, such as to also include the motivational aspect of emotions, a typical emotion regulation paradigm was combined with a Pavlovian learning paradigm in projects 1, 2 and 4 of the current thesis. Pavlovian learning was chosen as it represents the simplest form of associative learning, thus providing the possibility to combine the paradigm with emotion regulation without making the experiment too difficult for participants, as well as for interpreting potential results. Correspondingly, the most parsimonious model to account for Pavlovian learning is the Rescorla Wagner model, involving three parameters, prediction, prediction error, and learning rate (Pearce & Bouton, 2001; Rescorla & Wagner, 1972; Schultz & Dickinson, 2000). Given its simplicity, and the fact that the Rescorla Wagner model accounts for prediction error, the parameter that drives learning and might thus represent the motivational aspect of emotions, the chosen model provides an excellent basis for the study of emotion regulation in a wider context, as in projects 1, 2 and 4 of the current thesis.

It should be noted, however, that the Rescorla Wagner model can only account for classical conditioning, and cannot be used to explain other forms of associative learning, which humans commonly use, such as higher order associative learning or reinforcement learning (Ouden, 2009). Furthermore, associative learning can also be modelled by an alternative approach – the Bayesian learning models, which not only account for point estimates of learning-related associations, but also employ full posterior distributions, taking into account both the probabilities of associations and the uncertainty of these probabilities (Ouden, 2009). Bayesian learning models are more difficult to interpret, but have recently gained significance

and have also successfully been applied to Pavlovian and reinforcement learning (Behrens, Woolrich, Walton, & Rushworth, 2007; Chater, Oaksford, Hahn, & Heit, 2010; Courville, Daw, & Touretzky, 2006; Yoshida, Dolan, & Friston, 2008). In summary, while the Rescorla Wagner model is a sensible choice for modelling prediction errors in a classical conditioning study, it is important to carefully consider which models are best fitted for certain experimental paradigms and research questions. Future studies could address the question of whether emotion regulation influences prediction error-related brain processes in other forms of associative learning, such as reinforcement learning.

6.3.3 Psychotherapist as the Social Regulator

To extend the *regulation* part of emotion regulation, projects 3 and 4 of the current thesis used a psychotherapist to study effects of social reappraisal and social emotion modulation, respectively. When another person is regulating your emotions, your relationship and the person's significance in your life play an important role in how successful they might be at influencing your feelings. It is reasonable to assume that an established close relationship might lead to stronger and more successful social emotion regulation and modulation. However, it is equally important that the target of regulation interprets the regulator's intentions as positive. If the target believes that the regulator is helping them because they think them incapable of controlling their own emotions well, this could undermine the regulation success (Reeck et al., 2015).

A way to standardise the relationship with the regulator across participants is to use a newly acquainted individual, with whom all participants form a similar social connection within a predetermined time. It is naturally very difficult to form a meaningful bond with a stranger in a short time, but most people have positive preconceptions about psychotherapists (e.g., that they have experience with helping people feel better, that they can be trusted), and compared to an unfamiliar stranger, a psychotherapist is more likely to be perceived as both competent and warm – two main traits that determine the perception of another person on an initial encounter (Fiske, Cuddy, & Glick, 2007). Using a psychotherapist in a social emotion regulation experiment thus represents a good balance between social

connection strength and comparability across participants. However, it represents but one way to realise successful social emotion regulation. Future experiments could investigate the influence of social relationships on social regulation success, as well as possible differences in brain mechanisms supporting social emotion regulation when implemented by different regulators.

6.4 Future Directions

Projects of the current thesis offer a foundation for a number of potential future studies that could offer additional support for the extended account of emotion regulation and further expand the concept. The current section outlines three projects that build on studies from the current thesis by either employing alternative analysis methods or using novel paradigms to address specific research questions. The first proposed project expands the view of emotion regulation by using graph analysis to examine global whole-brain changes during intrapersonal and social cognitive emotion regulation. The second project addresses a fundamental aspect of social emotion modulation: can the presence of another affect your brain state even in the absence of emotional stimuli? Finally, the third study explores whether joint attention, an essential building block of social interaction, is crucial for successful social emotion modulation, such that it drives the success of modulation.

6.4.1 Global Brain Interaction Effects of Emotion Regulation

Existing neuroimaging studies on emotion regulation effects, including those of the current thesis, tend to focus on effects of emotion regulation on local changes in brain activity and/or connectivity. However, some neurobiological theories suggest that emotion regulation is in fact realised by increased interactions among global functional brain networks spanning the entire brain (Barrett, Wilson-Mendenhall, & Barsalou, 2014; Gross & Barrett, 2011; Lindquist & Barrett, 2012). In contrast to the conventional local activation and connectivity analyses based on the general linear model, graph theoretical analysis of structural and functional data allows one to examine the global structure of interactions among regions of the entire brain (Bullmore & Sporns, 2009). The proposed project would re-analyse intrapersonal

reappraisal and social reappraisal effects by employing graph analysis, to test the assumptions of global neurobiological theories.

The entire brain would be parcellated into functionally and structurally meaningful regions of interest, after which two graphs with nodes (i.e., brain regions) and edges (i.e., emotion-related functional connections between them) would be created, one for the regulation, and one for the no regulation condition. In line with global theories, two main hypotheses would be tested. First, modularity, a global measure of graph's decomposability into functional modules (Bullmore & Sporns, 2009), should remain stable across no regulation and regulation conditions, following the idea that similar functional brain networks support both types of emotional states (Barrett et al., 2014; Lindquist & Barrett, 2012). Second, global participation, a measure of connection strength between each node and nodes of other modules (Guimerà & Amaral, 2005), should increase during emotion regulation, reflecting an increased interaction between functional brain networks due to reappraisal (Barrett et al., 2014; Lindquist & Barrett, 2012). Using a different analysis method, the study would expand the view of emotion regulation by highlighting currently unknown global brain interaction effects of intrapersonal reappraisal and social reappraisal.

6.4.2 Social Emotion Modulation Effects on Intrinsic Brain States

Several studies have shown that when a person is exposed to threatening stimuli or find themselves in a threatening situation, the presence of a supportive person can attenuate aversive emotions and reduce stress (Conner et al., 2012; Eisenberger et al., 2011; Onoda et al., 2009; Younger et al., 2010). However, not much is known about the effects of social emotion modulation in the absence of threatening stimuli or any stimuli at all. It has been proposed that the presence of supportive conspecifics, in contrast to being alone, is potentially reflected by a fundamentally different brain state, potentially reflecting a reduction of general threat vigilance (Beckes & Coan, 2011; Coan, 2011; Coan & Sbarra, 2015). In line with this proposal, a recent study confirmed that activity in threat-sensitive regions was reduced by social emotion modulation during inter-trial intervals of an emotion experiment, i.e., in the absence of direct emotional stimulation (Zhang, Li, Beckes, & Coan, 2013).

However, effects of social emotion modulation on intrinsic brain networks, reflecting functional brain organisation during rest, i.e., in the absence of any external stimulation, remain unclear.

The proposed study would use independent component analysis to analyse data acquired during resting state (i.e., while participants lied in the scanner with their eyes closed in the absence of any input) in two conditions: a social presence condition, in which participants would have the feeling of being connected to a person outside the scanner, and an alone condition, in which they would be completely on their own. The analysis of differences between social and alone conditions would focus on the default mode network, due to its strong involvement in social-emotional processes (Amft et al., 2015; Mars et al., 2012; Schilbach et al., 2012). More specifically, changes during social emotion modulation might be focused on the dorsomedial PFC, a social safety-signalling region (Eisenberger, 2013), or on the anterior cingulate cortex, which is known to reflect associations between supportive social and threatening stimuli (Eisenberger, 2013; Zhang et al., 2013). Altogether, the proposed project would expand the view of emotion regulation by examining the effects of social emotion modulation on intrinsic functional brain states in the absence of any external stimulation.

6.4.3 Joint Attention as the Driving Force of Social Emotion Modulation

Despite many reports of social emotion modulation effectiveness (Conner et al., 2012; Eisenberger et al., 2011; Onoda et al., 2009; Younger et al., 2010), it remains unexplored exactly what part or parts of the social interaction are driving the modulation and what neural mechanisms support this process. One of the basic building blocks of a successful social interaction is the ability to share attention, also called joint attention (Moore & Dunham, 1995). Based on the idea that joint attention is especially important for trustful interactions in threatening situations, the proposed project would explore whether joint attention is the essential part of social emotion modulation, driving its effectiveness.

A combined eye tracking – fMRI experiment would be carried out, during which participants would interact with an avatar on the computer screen, convinced that

the avatar is being controlled by another participant they had just met. The set-up was recently developed to recreate a natural joint attention setting in an experimental MRI environment (Pfeiffer et al., 2014; Schilbach et al., 2010). In the proposed project, the set-up would be modified to additionally include a classical conditioning paradigm with electric shocks as unconditioned stimuli, to evoke fear. We would first test the hypothesis that joint attention is both relevant and necessary for successful social fear regulation. With the help of a Rescorla Wagner model, the project would additionally examine the underlying mechanisms by which joint attention is influencing fear processing: does joint attention attenuate fear by targeting prediction (i.e., fear-related) and/or prediction error (i.e., unexpected electric shock-related) processing? The effects might be centred on the ventral striatum and the anterior insula, realised via prefrontal and parietal control mechanisms (Mulej Bratec et al., 2015). The proposed project would expand our view of emotion regulation by way of determining the driving force of social emotion modulation and exploring the underlying neural mechanisms by which joint attention is affecting human fear processing.

6.5 Conclusion

To navigate the ups and downs of everyday life without too much turbulence, it is critical that we can effectively regulate our emotions. Emotion dysregulation, ranging from the inability to recognise the need for emotion regulation to choosing an inappropriate regulation strategy or wrongly implementing such strategy, can have dire consequences: a wide variety of affective disorders, such as major depression or anxiety, have been associated with problems in intrapersonal emotion regulation (Eftekhari et al., 2009; Gross & Jazaieri, 2014; Sheppes et al., 2015). Lacking the means for social emotion regulation and modulation can be even more devastating: inadequate social relationships are associated with a mortality risk that is as high as that of smoking (Holt-Lunstad et al., 2010). It is thus essential that we continue to expand our knowledge of emotion regulation, both in healthy individuals, as well as in relation to affective disorders and disorder-specific emotional and social impairments.

The current thesis complements and enhances our current understanding of emotion regulation. It offers original findings on the effects of intrapersonal reappraisal, social emotion modulation and social reappraisal on both basic emotional response-related and motivational prediction error-related brain activity and connectivity. Furthermore, by adding to both the *emotion* and the *regulation* part of the conventional view of emotion regulation, the thesis offers a new perspective of emotion regulation that can serve as a foundation for future studies. All in all, the thesis provides a small but relevant piece to the puzzle of emotion regulation, which could ultimately lead to successful treatment of disorders hallmarked by problems with emotion regulation (such as major depression and anxiety disorders) and/or difficulties with social interactions (such as autism spectrum disorders).

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EIDESSTATTLICHE VERSICHERUNG/AFFIDAVIT

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation 'Extending the Concept of Emotion Regulation with Model-Based fMRI' selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

I hereby confirm that the dissertation 'Extending the Concept of Emotion Regulation with Model-Based fMRI' is the result of my own work and that I have only used sources or materials listed and specified in the dissertation.

Munich, 25 May 2016 Satja Mulej Bratec

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The author of this thesis is the first author of the manuscript. **S.M.B.** and C.S., with the help of G.S. and C.Z., conceived the experiment. **S.M.B.** recruited and trained participants, and **S.M.B.** and X.X. together conducted behavioural and fMRI data acquisition. **S.M.B.** analysed behavioural and imaging data, with some help from X.X. and A.D., and under the supervision of A.W. and V.R. **S.M.B.**, supervised by C.S., wrote the manuscript, which was commented on and revised by L.S.

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