MAX PLANCK INSTITUTE FOR HUMAN COGNITIVE AND BRAIN SCIENCES LEIPZIG

Philipp Kanske: Neural bases of emotional processing in affective disorders.
Leipzig: Max Planck Institute for Human Cognitive and Brain Sciences, 2014
(MPI Series in Human Cognitive and Brain Sciences; 160)

Neural bases of emotional processing in affective disorders

Impressum

Max Planck Institute for Human Cognitive and Brain Sciences, 2014

Druck: Sächsisches Druck- und Verlagshaus Direct World, Dresden
Titelbild: © Dice with emotion faces – Maxx-Studio (Shutterstock.com), 2014

ISBN 978-3-941504-44-8

Aus dem Institut für Neuropsychologie und Klinische Psychologie

(Wissenschaftliche Direktorin: Prof. Dr. Herta Flor)

des Zentralinstituts für Seelische Gesundheit

Neural bases of emotional processing in affective disorders

Kumulative Habilitationsschrift

zur Erlangung der Venia legendi für die Fächer

Klinische Psychologie, Biologische und Neuropsychologie, Medizinische Psychologie

der Hohen Medizinischen Fakultät Mannheim

der Ruprecht-Karls-Universität Heidelberg

vorgelegt von

Philipp Kanske

aus Dresden

2013

Contents

1 Introduction 1

2 Theoretical and empirical background 3

2.1 Neural bases of emotional processing 3

2.2 Emotion-cognition interactions 5

2.2.1 Cognitive regulation of emotion 5

2.2.2 Emotional influence on cognitive processing 7

2.2.3 Biased information processing 8

2.3 Emotional processing and interactions with cognition in affective disorders 9

3 Questions and hypotheses 15

4 Work program and methods 19

5 Experiments 23

5.1 Neural correlates of emotion regulation in healthy participants, remitted patients with depression, euthymic bipolar patients and unaffected relatives of bipolar patients 23

5.2 Neural correlates of emotional distractibility in healthy participants, euthymic patients with bipolar disorder, unaffected relatives of bipolar patients and healthy individuals with hypomanic personality 91

5.3 Electroencephalographic correlates of biased information processing 123

6 General discussion 137

6.1 Summary 137

6.2 Implications 139

6.3 Critique and conclusions 144

7 References 147

Acknowledgments 173

1 Introduction

Affective disorders are critically characterized by altered emotionality, from excessive negative emotions and mood during depression, to peaks in positive emotions during mania. Understanding the neural correlates of these alterations is highly relevant for the development of etiological models, which could in the future yield earlier diagnosis and novel treatment approaches. The last years have already seen a surge in studies targeting the neural mechanisms underlying emotional processing in general and in patients with affective disorders in particular (Bourke, Douglas, & Porter, 2010; Phillips, Ladouceur, & Drevets, 2008). Relatively little is known, however, about the reciprocal influence of emotional and cognitive processes in these disorders, even though their essential connectedness has clearly been demonstrated in healthy populations (Kanske, 2012; Pessoa, 2008).

Emotional responses do not unfold uniformly, but are subject to change through cognitive regulation mechanisms, for example appraisal and reappraisal processes or attentional control mechanisms (Ochsner & Gross, 2005). As impairments in cognitive control abilities have been consistently observed in depression and bipolar disorder (Arts, Jabben, Krabbendam, & van Os, 2008; Austin, Mitchell, & Goodwin, 2001), their regulatory influence on emotion may be impaired as well, which could potentially explain part of the affective alterations. In turn, cognitive impairments may also partially result from excessive emotional responses whose regulation draws on shared resources, thereby yielding enlarged distraction effects. Lastly, predominance of negative or positive emotions can bias cognitive processes. Such, more negative or positive interpretations of ambiguous situations have been reported to be essential for the onset and maintenance of affective disorders (Mathews & MacLeod, 2005). However, experimental paradigms to study biases implicitly are still missing.

A crucial question is what role emotional and emotional-cognitive impairments play in the development and course of affective disorders. They may represent markers of increased vulnerability if they are already present before the onset of depression or bipolar disorder (Gottesman & Gould, 2003; Leboyer et al., 1998). Studies in healthy relatives of patients with an affective disorder, who have in increased genetic risk to develop a disorder themselves, but are still unaffected by the illness, have indeed shown abnormal processing of affective stimuli and cognitive impairments (Arts et al., 2008; Surguladze et al., 2010). There is little evidence, however, on the interactions of emotion and cognition. On the other hand, impairments may also represent consequences of an affective disorder, rather than a vulnerability, and only show after illness onset. If they persist into remission, these impairments could be a reason for

the high relapse rates (Keck et al., 1998; Tohen et al., 2003), which would make them a special target of treatments.

The studies included in this thesis aimed at extending our knowledge of the neural correlates of emotional processing in affective disorders, in particular of the interactions of emotional and cognitive processes. Section 5.1 presents studies that investigated two different types of cognitive control over emotions in healthy volunteers and patients with remitted depression and euthymic bipolar patients. To further elucidate if emotion regulation impairments represent a vulnerability marker, unaffected relatives of bipolar patients were also tested. Section 5.2, in contrast, includes two studies that tested how emotional stimuli affect cognitive processing in a mental arithmetic task. Here, euthymic bipolar patients, unaffected relatives of bipolar patients and healthy individuals with hypomanic personality were tested in addition to healthy control participants. Lastly, a study on a paradigm that allows indirect investigation of biases in cognitive processing is presented in Section 5.3. Here, healthy individuals were tested and it was probed how biases are associated to inter-individual variations in depression related traits.

2 Theoretical and empirical background

The present chapter aims at giving the theoretical and empirical background for the research questions that were addressed in the presented studies. It first introduces the concept of emotions including its neural underpinnings and then discusses how emotional and cognitive processes are reciprocally influencing each other. It concludes with a section on our current understanding of alterations in these mechanisms in patients with affective disorders and leads over to the research questions, which are raised in the next chapter.

2.1 Neural bases of emotional processing

There is a multitude of definitions for what emotions are, the most critical components being that they are episodic in nature and form psycho-physiological reaction patterns, that is, they always incorporate multiple levels from peripheral physiological to central nervous and subjective responses (Gall, Kerschreiter, & Mojzisch, 2002). Emotions result from the evaluation of a stimulus regarding its relevance for the goals and needs of an organism (Clore & Ortony, 2000; Keltner & Gross, 1999). If judged as relevant, an emotion is elicited, including an action tendency, which is energized by the accompanying physiological changes (Frijda, 1994). Therefore, emotions are highly adaptive mechanisms, which allow more flexible behavior than simple reflexes, but are still faster than elaborate cognitive information processing (Scherer, 1994). If aberrant, however, emotions may cause inadequate responses, due to the dysfunctional evaluation of the relevance of a stimulus, as is seen in patients with affective disorders (see Section 2.3). The definition also highlights the importance of appraisal processes for the development of an emotion, since it is the evaluation of a stimulus with regard to goals and needs that elicits an emotional response, thus foreshadowing potential interactions of emotional with cognitive processes (see Section 2.2).

Regarding the neural underpinnings of emotional processing, the most recent models shift more and more to networks of regions that interact to detect emotional stimuli and generate an emotional response (Pessoa & Adolphs, 2010). Nevertheless, one of the most important hubs seems to be the amygdala, a group of nuclei in medial temporal cortex (LeDoux, 2007). Lesions of the amygdala lead to a loss in emotional reactivity, for example in showing fear of dangerous objects, and disrupt social behavior in animals (Kluver & Bucy, 1937; Meunier, Bachevalier, Murray, Malkova, & Mishkin, 1999; Weiskrantz, 1956) and humans (Aggleton, 1992; Terzian & Ore, 1955). Also, recognizing emotions in faces and social stimuli is impaired, when the amygdala is not intact (Adolphs, Tranel, Damasio, & Damasio, 1994). Similarly,

direct recordings from the amygdala show its sensitivity to social and emotional stimuli in different sensory modalities (Leonard, Rolls, Wilson, & Baylis, 1985). The vast neuroimaging literature corroborates this. Meta-analyses of amygdala function demonstrate its involvement in the processing of positive as well as negative emotional stimuli (Sergerie, Chochol, & Armony, 2008).

The amygdala is well connected and receives input from sensory cortices as well as through direct subcortical thalamic projections (Blanchard & Blanchard, 1972; LeDoux, 1995; Tamietto, Pullens, de Gelder, Weiskrantz, & Goebel, 2012), which enables it to very rapidly detect basic emotional features in stimuli. This feature selection seems to be highly plastic as shown in cortical blindness with complete loss of visual evoked event-related electroencephalographic responses (Hamm et al., 2003; Morris, Ohman, & Dolan, 1999). Fear conditioning to visual stimuli is still possible in these patients and results in a potentiated startle response, an amygdala mediated mechanism (Grillon, Ameli, Woods, Merikangas, & Davis, 1991). Projections from the amygdala are to sensory areas, where they can amplify processing of emotional over non-emotional stimuli, and also prefrontal cortex, including orbitofrontal and anterior cingulate cortex (Whalen & Phelps, 2009).

A critical structure for processing of positive emotion and reward in particular is the nucleus accumbens (or ventral striatum) (Burgdorf & Panksepp, 2006; Haber, 2011; Haber & Knutson, 2010). It is sensitive to errors of reward prediction (Pagnoni, Zink, Montague, & Berns, 2002), even if the omissions of expected reward were not consciously perceived (Berns, Cohen, & Mintun, 1997). There is also evidence for a subcortical route to the nucleus accumbens (McHaffie, Stanford, Stein, Coizet, & Redgrave, 2005), which has led to the suggestion that amygdala and nucleus accumbens are the main processors of non-conscious emotion detection (Tamietto & de Gelder, 2010). Their input is essential for conscious processing of emotions, which requires involvement of cortical regions such as orbitofrontal and anterior cingulate cortex.

The anterior cingulate cortex is very consistently activated in experimental tasks with emotional stimuli (Dalgleish, 2004). It has been hypothesized to be functionally segregated into a ventral portion that is mainly involved in emotional processing and a dorsal cognitive portion that is more engaged in executive attentional control (Bush, Luu, & Posner, 2000). More recent views, however, discuss both portions as relevant for emotion processing (Etkin, Egner, & Kalisch, 2011). While the ventral portion is supposed to mainly underlie implicit regulatory processes of emotion generating limbic regions (Etkin et al., 2011), the dorsal portion is engaged in conscious appraisal processes (Kalisch, Wiech, Critchley, & Dolan, 2006) and the expression of emotion (Gentil, Eskandar, Marci, Evans, & Dougherty, 2009).

Other regions that are involved in emotional processing are the anterior insular, orbitofrontal and ventromedial prefrontal cortices (Phan, Wager, Taylor, & Liberzon, 2002). The anterior insula, in particular, is a center for interoceptive re-represention and as such discussed as critical for the generation of subjective feeling (Craig, 2009). It is also crucial for understanding and sharing the emotions of others (Singer, 2012).

The time-course of processing emotional stimuli has been extensively studies using event-related potentials of the electroencephalogram (Hajcak, MacNamara, & Olvet, 2010). This research shows that emotions are recognized very early on with amplitude differences already approximately 200 ms after presentation onset of a stimulus (Vuilleumier & Pourtois, 2007). Interestingly, this has been shown across different types of stimulus categories, such as faces, pictures or words (Ashley, Vuilleumier, & Swick, 2004; Kanske & Kotz, 2007; Olofsson, Nordin, Sequeira, & Polich, 2008) and across different modalities, including visual and auditory (Citron, 2012; Schirmer & Kotz, 2006). Indexing the sustained effects of emotion on stimulus processing, a late positive potential is also consistently observed to be increased for emotional over neutral material (Olofsson et al., 2008). It typically starts around 300 ms after stimulus onset and peaks between 500 and 800 ms. Even when controlling arousal levels, the late positive potential is sensitive to emotion in stimuli (Kaestner & Polich, 2011; Rozenkrants & Polich, 2008) and also differentiates between positively and negatively valenced material (Schacht, Adler, Chen, Guo, & Sommer, 2012). Some evidence also relates it to the subjective intensity ratings of emotion (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000).

2.2 Emotion-cognition interactions

Emotional responses do not evolve uniformly, but are subject to influence through cognition (Gross, 2002). Conversely, emotions also influence cognitive processing (Pessoa, 2008). This Section discusses these reciprocally interactive processes.

2.2.1 Cognitive regulation of emotion

Emotion regulation is not a coherent concept and the term refers to a number of different strategies that can be applied to regulate emotion. A largely accepted definition includes all of “the ways individuals influence which emotions they have, when they have them, and how they experience and express these emotions” (Gross, 1999). The variations in how successfully individuals achieve regulation of their emotions are highly significant, also in a subclinical range, as they predict well-being, income, and socio-economic status (Cote, Gyurak, & Levenson, 2010). Among

adolescents, emotion regulation is related to the amount of victimization among peers, friendship support, and family cohesion (Adrian et al., 2009). Even enhanced physical health is reported by individuals with better emotion regulation skills (Consedine, Magai, & Horton, 2005). The strategies that people apply to regulate emotions vary in their degree of functionality, for example, several studies have shown that modulating the expression of an emotion through suppression does not change the emotion itself, or rather has detrimental effects leading to increased physiological responding (Drabant, McRae, Manuck, Hariri, & Gross, 2009; Egloff, Schmukle, Burns, & Schwerdtfeger, 2006). Other, more adaptive regulation strategies have been thoroughly investigated as well, the most prominent example being reappraisal. It is a strategy of cognitive change, referring to the reinterpretation of the meaning of a situation, which yields an altered emotional response (Kalisch, 2009). This includes subjective emotionality as well as physiological measures such as facial muscle activity or the startle reflex (Ray, McRae, Ochsner, & Gross, 2010). A strategy drawing more on attentional control is distraction from the emotional aspects of a scene. For example, performing a demanding memory task or mental arithmetic will reduce the emotional response, even if the emotional stimulus is constantly present (Van Dillen, Heslenfeld, & Koole, 2009). Interestingly, some mechanisms have emotion regulatory effects, even though they do not primarily aim at modulating the emotional experience. Affect labeling, for example, which refers to using words to characterize feelings or the emotional aspects of an event, reduces the subjective and physiological intensity of emotional responses (Lieberman et al., 2007). Similarly, the paradoxical effect of acceptance of an emotion is a reduction of subjective current emotion intensity (Levitt, Brown, Orsillo, & Barlow, 2004) and physiological responding (Campbell-Sills, Barlow, Brown, & Hofmann, 2006). While these strategies rely on very different psychological mechanisms, their modulating effects on emotional processing are very similar. This also seems to be the case for the neural mechanisms underlying emotion regulation.

Regarding its neural underpinnings, the concept of emotion regulation translates into inhibitory and facilitatory interactions of control and regulated networks that are relatively well understood. As discussed in the previous section, some brain regions are crucially involved in the generation of emotion; the most prominent example is the amygdala. Using the regulation strategies described above, participants in experimental settings can modulate activity in the amygdala (Ochsner & Gross, 2005), for example, activation is reduced for the same sensory input when reappraising a stimulus as less threatening compared to simply viewing it (Eippert et al., 2007). This effect is driven by a network of brain regions, critically including dorsolateral and medial prefrontal cortices. Examining the connectivity between the regulating control network and amygdala shows a negative coupling during regulation, that is, stronger increase in control activity is accompanied by larger reductions in amygdala activation

(Walter et al., 2009). These connections from control regions to the amygdala may be direct, but seem to be partly indirect with intermediate brain areas (Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008). There is some evidence showing the commonalities of this principle functioning across different regulation strategies, even though studies directly comparing strategies are still rare (Goldin & Gross, 2010; McRae et al., 2009). Such investigations, however, would be of great clinical importance to identify those strategies that patients can not apply adequately as treatment targets and those techniques that patients are not impaired in as resources.

2.2.2 Emotional influence on cognitive processing

Emotion can have both a facilitatory, but also an interfering influence on cognitive processing (Kanske, 2012; Pessoa, 2008). If task-relevant, an emotional stimulus can induce better performance, for example regarding memory (Dolcos, LaBar, & Cabeza, 2004; Hamann, 2001) or cognitive control tasks (Kanske & Kotz, 2011b, 2011c), independently of the valence of the stimulus (Kanske & Kotz, 2010, 2011a, 2011d). In contrast, if an emotional stimulus is task-irrelevant and presented, for example, shortly before a cognitive control task (Hart, Green, Casp, & Belger, 2010; Padmala & Pessoa, 2011) or during the encoding period in a working memory task (Dolcos, Kragel, Wang, & McCarthy, 2006; Dolcos & McCarthy, 2006), performance in that task is impaired.

The neural mechanisms underlying facilitatory influences are partly separate for different functions, because they involve the networks that are specific to the cognitive task at hand. For memory enhancement, this includes structures in the medial temporal lobe, the hippocampus and associated parahippocampal regions (Dolcos et al., 2004), while it is mainly the anterior cingulate cortex for cognitive control improvements (Kanske & Kotz, 2011c). The amygdala, which is involved across different types of tasks, seems to be crucially triggering modified processing in these networks, for example, through increased connectivity to the ventral portion of the anterior cingulate cortex when emotion is detected in a cognitive control task (Kanske & Kotz, 2011b) or to the hippocampus when emotional stimuli are to be remembered (Dolcos et al., 2004). With regard to interfering effects of emotion, they also involve the particular neural networks involved in the specific function that is impaired. However, the evidence regarding the nature of this influence is inconsistent. Some studies reported an increase in activation of task-relevant brain regions, potentially indicating compensatory activation to preserve goal-directed behavior (Blair et al., 2007; Hart et al., 2010; Pereira et al., 2010). Several other studies, however, found reduced activation in task-related regions, which was interpreted as emotion taking the cognitive system ‘off-line’ (Anticevic, Repovs, & Barch, 2010;

Dolcos et al., 2006; Dolcos & McCarthy, 2006; Mitchell et al., 2008). A shortcoming of these studies is that they did not directly test if the hyper- and hypo-activations were really located in the neural networks that are essential and specific to the processing of a certain cognitive task. Therefore, the activation changes due to emotion in these studies may not be directly related to the task, but to another concurrent process. Sophisticated functional localization of specific networks, before testing the influence of emotion on them would allow better delineation of the mechanisms underlying emotional distractibility. The clinical relevance lies mainly in the fact that patients with affective disorders are often characterized by cognitive deficits, which might be partially explained by inadequate emotion-cognition interactions.

2.2.3 Biased information processing

Another mechanism of emotion-cognition interactions is a biasing influence that emotion exerts on cognitive information processing. Typically this has been investigated through interindividual differences in emotional state, for example in the presence of dysphoric mood, or through the induction of an emotional state, for example with the help of affective pictures, music or mental imagery. Such biased processing has been demonstrated for a range of different cognitive functions. Dysphoric individuals attend longer to the spatial locations of negative emotional cue stimuli in Posner type cueing paradigms (Koster, De Raedt, Goeleven, Franck, & Crombez, 2005) and also show memory biases for negative emotional words (Gilboa & Gotlib, 1997). Inducing emotion also affects attentional mechanisms, for example positive emotion induction yields attentional broadening as measured in viewing time and saccades to positive stimuli (Wadlinger & Isaacowitz, 2006), and memory for mood congruent items (Chepenik, Cornew, & Farah, 2007). Furthermore, emotion induction increases the interference effects of emotional stimuli on cognitive processing (Isaac et al., 2012) and also biases socio-affective processing, such that the recognition of emotion in faces is influenced (Chepenik et al., 2007), as are the judgments about other people based on short person descriptions (Forgas & Bower, 1987). The effects of emotion induction are even measurable in an individual's plans for future negotiations with others and in the subsequent bargaining outcomes that are attained (Forgas, 1998). Interestingly, these studies also clearly dissociate the effects of positive and negative emotion induction (Forgas, 1998; Forgas & Bower, 1987).

The investigations listed above show mood-congruent biasing of valenced stimuli, however, biased information processing may have its most critical impact in the interpretation of ambiguous stimuli. Such decision making under uncertainty also has a particular potential to reveal the biasing influence that emotion can have on

cognition, as ambiguous stimuli are free of affordances and, thus, any response to them is entirely driven by internal factors. An experimental approach to studying decision making under ambiguity has recently been tested in animals (Harding, Paul, & Mendl, 2004). Rats were given food when they pressed a lever after hearing one specific tone; another tone was paired with aversive white noise, if the rat failed to press a separate lever. After learning these responses, tones that were intermediate in frequency compared to the other two tones were presented additionally and responses to these ambiguous stimuli were taken as an indicator for a positive bias if the rats pressed the lever associated with food more often or as a negative bias if the lever associated with the white noise was pressed more often. Most interestingly, this study also tested animals kept in unpredictable housing, which induces symptoms of a mild depression-like state (Willner, 1997; Zurita, Martijena, Cuadra, Brandao, & Molina, 2000). These animals showed a negative bias in this scenario. Similarly, congenitally helpless rats, that also constitute an animal model of depression, also show a negative bias (Enkel et al., 2010). In this study, a pharmacological stressor also had an effect on normal rats and biased rats away from positive responding.

The only study in humans that utilized a similar paradigm reported a correlation of the size of a negative bias with trait anxiety measures assessed in questionnaires (Anderson, Hardcastle, Munafo, & Robinson, 2012). However, in this study the intermediate tones were also reinforced, which renders them non-ambiguous. The study, therefore, did not allow for the detection of an inherent interpretation bias. Fully adopting this paradigm for research in humans would have the advantage that it enables translational investigation of biased information processing and, thus, testing the neural underpinnings of these mechanisms on multiple levels including the cellular and molecular levels (Enkel et al., 2010).

2.3 Emotional processing and interactions with cognition in affective disorders

Changes in emotional processes are defining characteristics of affective disorders. The most recent version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013) lists abnormally and persistently elevated, expansive or irritable mood or depressed mood for most of the day as the A-criteria for manic and depressive episodes, respectively. These alterations are measurable in self-reports (Altman, Hedeker, Peterson, & Davis, 1997; Beck, Steer, & Carbin, 19888; Lovibond & Lovibond, 1995; Page, Hooke, & Morrison, 2007) and observer ratings (Hamilton, 1960; Williams, 2001; Young, Biggs, Ziegler, & Meyer, 1978), but also in experimental investigations. For example, currently and previously depressed patients show greater reactivity to negative mood induction (Ingram, Bernet, & McLaughlin, 1994; Segal et al., 2006; Timbremont & Braet, 2004) and bipolar

patients report more positive emotion even after neutral mood induction (M'Bailara et al., 2009). Similarly, responses to brief emotional stimulation are altered in depression (Dichter & Tomarken, 2008; Dichter, Tomarken, Shelton, & Sutton, 2004) and bipolar disorder (Giakoumaki et al., 2010).

These changes are mirrored by generally increased amygdala activity in depression (Drevets et al., 1992) and bipolar disorder (Drevets et al., 2002). Such alterations could also be specified for responding to emotional stimuli, for example, using emotional faces that were masked by subsequently presented neutral faces increased activity in the amygdala to all faces, but in particular to fearful ones was found (Sheline et al., 2001). Thus, even if the stimuli are not perceived consciously, hyperactivity in emotion generating regions can be observed. This result of elevated amygdala responding to emotional stimuli could be replicated with emotional words on which participants performed personal relevance ratings (Siegle, Thompson, Carter, Steinhauer, & Thase, 2007) or with consciously perceived emotional faces on which participants performed gender decisions (Surguladze et al., 2005). However, there are also studies that did not observe differences in amygdala activity for emotional vs. neutral video stimuli (Beauregard et al., 1998) or static face stimuli (Frodl et al., 2009) when comparing currently depressed patients with healthy controls. Also, recent meta-analyses differ in their results regarding amygdala hyperactivation in depression (Delvecchio et al., 2012; Diener et al., 2012). Similarly, there are a number of investigations on bipolar disorder that show increased reactivity of the amygdala to emotional faces when currently depressed (Almeida, Versace, Hassel, Kupfer, & Phillips, 2010; Altshuler et al., 2008) or manic (Altshuler et al., 2005). Also other stimulus categories such as images with emotion-evocative captions elicit elevated amygdala responses in bipolar patients (Malhi et al., 2004). As for depression, however, there are also reports of normal amygdala responding to emotional stimuli in bipolar disorder (Foland-Ross et al., 2012; Liu et al., 2012). Meta-analyses seem to yield more support for amygdala hyperactivation in bipolar disorder (Delvecchio et al., 2012; Houenou et al., 2011), but unilateral hypoactivation has also been shown (Chen, Suckling, Lennox, Ooi, & Bullmore, 2011).

A specific of the described studies is that none of them explicitly instructed participants to directly *regulate their emotional responses*. This may in part explain the variance in the results, as there are differences in the habitual use of emotion regulation between patients with affective disorders and healthy individuals. Questionnaire studies show that depressed and bipolar patients report to use adaptive emotion regulation strategies less frequently and maladaptive ones more frequently than healthy participants (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Green et al., 2011). Without explicit regulation instructions, patients and healthy controls may, thus, have dealt differently with arising emotions in the experimental settings. In depression

there are a few studies that tested the influence of explicit emotion regulation instructions on emotional responses. They showed that down-regulation of the amygdala through a reappraisal strategy is impaired in currently depressed patients (Beauregard, Paquette, & Levesque, 2006) and that the connectivity of the amygdala to prefrontal regions during reappraisal is altered (Erk et al., 2010; Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007). Interestingly, none of these studies found amygdala hyperactivity to emotional stimuli in the simple viewing condition, but only in the regulation conditions, which is in line with the suggestion that the diverse results regarding amygdala activity may be explained by different implicit application of emotion regulation. With regard to unipolar depression, the previous studies raised several questions. First, it is unclear if the observed deficit in amygdala regulation through reappraisal generalizes to other regulation strategies or is specific. Second, all previous studies tested acutely depressed patients. Therefore, it is open, if the deficit is state-dependant or has characteristics of a trait-marker and is still present in remitted patients. Third, the relation of the observed deficits in amygdala regulation and the self-reports of infrequent use of habitual reappraisal use is unclear. And fourth, since previous studies tested the regulation of negative emotion only, it is unclear if the deficits are also present for positive emotional stimuli. At the time the present studies were conducted, there were no published reports on the neural correlates of emotion regulation deficits in bipolar disorder. Thus the raised questions also apply to bipolar disorder, in addition to the more fundamental question if there are impairments at all in experimental settings.

Cognitive deficits have been described in depression (Levin, Heller, Mohanty, Herrington, & Miller, 2007; Paelecke-Habermann, Pohl, & Leplow, 2005) and bipolar disorder (Bora, Yucel, & Pantelis, 2009; Malhi et al., 2007), but seem to be more pronounced and severe in patients with bipolar disorder (Gualtieri & Morgan, 2008; Sweeney, Kmiec, & Kupfer, 2000). As it has been consistently shown that *emotional distracters* have a particularly strong impact on cognitive processing when compared to neutral distracters (Dolcos et al., 2006; Hart et al., 2010) and given the emotional perturbations in bipolar disorder described above, the question arises whether the cognitive deficits are, at least in part, due to these changes in emotional processing (Henin et al., 2009; Strakowski, Delbello, & Adler, 2005). Several studies investigated cognitive task performance in the presence of emotional distracters. Two studies using emotional Stroop tasks found abnormally increased frontal and limbic activity in bipolar patients during color naming of emotional compared with neutral words (Lagopoulos & Malhi, 2007; Malhi, Lagopoulos, Sachdev, Ivanovski, & Shnier, 2005). In these studies, emotion did not affect color naming reaction times in patients and in comparison subjects, suggesting that task processing was not directly influenced. Similarly, a study with an emotional go/no-go task yielded behavioral distraction effects in the emotional compared with the neutral condition, but no differences

between bipolar disorder and controls, although activation was increased in frontal and limbic regions (Wessa et al., 2007). Activation increases without behavioral effects were also found in working memory tasks with sad mood induction (Deckersbach et al., 2008) and face distracter stimuli (Bertocci et al., 2012). In addition to the lack of behavioral differences between patients and controls, these studies could also not clarify whether the observed hyperactivations reflect altered processing of the cognitive tasks (e.g. as a compensatory effect) or simply aberrant emotional processing. Addressing this issue would require the independent definition of the relevant task network before studying the influence of emotion on this network. Better understanding of the nature and causes of cognitive deficits in bipolar disorder is of great importance, as the number of deficits in executive function, attention and memory in these patients is correlated with the level of psychosocial functioning (Martinez-Aran, Vieta, Colom, et al., 2004; Martinez-Aran, Vieta, Reinares, et al., 2004) and only 24% of the patients achieve functional recovery in the first year after recovery (Keck et al., 1998), a rate that rises to only 43% after two years (Tohen et al., 2003).

Biased information processing has also been discussed as highly relevant for the development and maintenance of affective disorders (Mathews & MacLeod, 2005). While healthy individuals typically show a positive bias in attention, memory and particularly in the interpretation of ambiguous situations (Cummins & Nistico, 2002), cognitive theory of depression, for example, proposes that negative schemata (i.e. dysfunctional mental representations about the self, the world and the future) trigger mood-congruent interpretations of ambiguous situations, which in turn influences the emotional state (Beck, 2008). The resulting interplay of negative interpretations and emotions may be a cause for the development of affective disorders (Mathews & MacLeod, 1994). Previous investigations regarding this question, however, yielded partly inconsistent results. A study using ambiguous scenarios, for example, could demonstrate a negative bias in depression (Berna, Lang, Goodwin, & Holmes, 2011). The study presented putatively ambiguous sentences such as “You wake up, get out of bed, stretch and really notice how you feel today” and participants were asked to fully imagine the situation and then rate how pleasant or unpleasant they felt. These ratings were significantly related to depression scores. Also, when participants were asked to describe what outcome they had imagined, these outcomes were evaluated as more negative in the group scoring higher in depression by independent raters. A critical point may be that the scenarios used in this study were preselected from a larger pool of items on the basis of their ability to separate a high from a low depression group. Thus, it is not clear whether the results would generalize to other situations. Making use of the potentiation of the startle reflex by negative emotion, another study also found evidence for a negative bias in depression (Lawson, MacLeod, & Hammond, 2002). Neutral and negative words, for example “dress” and “stress”, were

acoustically merged to create ambiguous stimuli. Participants were instructed to imagine a situation triggered by their interpretation of the ambiguous stimulus and startle probes were presented in that time-window. Startle blink reflexes to the ambiguous words were larger in participants high in depression, suggesting that they interpreted the words more negatively. Conversely, another study found a slight positive bias in high depression participants (Lawson & MacLeod, 1999). Here, the latencies to read aloud neutral or negative target words that followed target-valence-congruent or ambiguous prime sentences were measured. The group high in depression scores did not show naming facilitation for the negative target words, but rather a pattern that results from an attenuated tendency to impose the more negative interpretations. The variance in the results of these studies may be due to stimulation and design differences. It seems, therefore particularly promising to try assessing the bias with an indirect measure that does not build on previously established associations, as is the case with affective prime sentences or valenced words. The alternative experimental approach described in Section 2.2.3 would allow for this and has been shown to relate the measured bias to animal models of depression such as congenital helplessness or unpredictable housing (Enkel et al., 2010; Harding et al., 2004). Beyond the advantage that adopting this paradigm for human research would have in enabling translational investigation of biased information processing, it is also a design that measures the bias indirectly and without making use of stimuli with pre-established positive or negative associations. In contrast, these associations are experimentally created and fully controlled. Transferring this paradigm to human research is, therefore, an important next step for improving our understanding of biased information processing and its relevance for affective disorders.

3 Questions and hypotheses

The described theoretical and empirical background raises several research questions that were addressed in the present thesis. They entwine around the central topic of reciprocal interactions of emotion and cognitive control, their neural correlates and, in particular, their potential alterations in unipolar depression and bipolar disorder. Furthermore, their role as a vulnerability marker for or as a consequence of bipolar disorder is investigated.

The three major topics are, first, how cognitive control can influence emotion. In contrast to implicit or automatic regulation of emotion (Phillips, Ladouceur, et al., 2008), cognitive regulation of emotion refers to using attentional control or cognitive change strategies to directly modulate the impact of emotionally evocative stimuli (Ochsner & Gross, 2005). This question is only little investigated in affective disorders, with more studies being done on depression (Beauregard et al., 2006; Erk et al., 2010; Johnstone et al., 2007) or only on a questionnaire, not an experimental level (Green et al., 2011). Second, increased emotional reactivity in bipolar disorder (Almeida et al., 2010; Altshuler et al., 2005) might have an influence on cognitive functioning. Cognitive impairments are a widely observed symptom in bipolar disorder (Henin et al., 2009), but their direct relation to altered processing efficiency in task-related neural networks under emotional distraction could not yet be demonstrated (Malhi et al., 2005; Wessa et al., 2007). Third, a negative bias in information processing leading to more negative interpretations of ambiguous situations and, thus, increasing negative emotion has been discussed as one of the mechanisms leading to the development and maintenance of depression and biases may also play a role for bipolar disorder (Beck, 2008; Mathews & MacLeod, 1994, 2005). Because previous investigations yielded partly inconsistent results, new paradigms to address this questions, which also allow for translational investigations, should be developed and validated (Enkel et al., 2010; Harding et al., 2004).

1. Do euthymic bipolar disorder patients and patients with remitted depression show impairments in voluntary emotion regulation through reappraisal and distraction and what are the neural correlates of such impairments?

   Hypothesis: Euthymic patients with bipolar disorder and patients with remitted depression show deficits in regulating their emotions through reappraisal as well as distraction. This should be reflected in a smaller reduction of their ratings of subjective emotional experience compared to the healthy control participants. Furthermore, it should show in reduced down-regulation of emotion generating

regions, in particular the amygdala, when the regulation strategies are applied compared to the healthy control participants. Activity in the regulating control network should also be altered and show either increases or decreases compared to healthy control participants. Inverse functional coupling between emotion generating and regulating regions is expected in the healthy control participants, but not in the patient groups.

2. Are potential emotion regulation deficits in bipolar disorder a vulnerability marker for the disorder and present in a population at high-risk to develop bipolar disorder, that is, unaffected first-degree relatives of bipolar disorder patients?

   Hypothesis: Unaffected first-degree relatives of bipolar disorder patients show similar deficits in emotion regulation as patients with bipolar disorder when compared to matched healthy control participants, which is reflected in subjective ratings, neural activity in emotion generating and regulating regions, as well as connectivity between the latter two.

3. Do euthymic bipolar disorder patients show increased emotional distractibility when performing a cognitive task? And are such distraction affects accompanied by changes in the neural correlates of processing the task at hand?

   Hypothesis: Euthymic patients with bipolar disorder show enlarged impairment in cognitive task processing when emotional distracters are presented simultaneously when compared to neutral distracters and compared to healthy control participants. This should be reflected in increased response times and error rates in the emotional distraction condition and altered activity in the neural network underlying processing of the task. Hyperactivation could indicate compensatory effects, while hypoactivation could reflect a breakdown of task-related activity.

4. Is the potentially increased emotional distractibility in bipolar disorder a vulnerability marker or a consequence of the disorder, that is, is it present in high-risk populations as well or can it only be observed in patients with at least one episode of the illness?

   Hypothesis: Unaffected first-degree relatives of patients with bipolar disorder and healthy individuals with hypomanic personality show the same increased emotional distractibility as patients with bipolar disorder, when compared to their healthy matched control participants, which is reflected in behavioral performance and neural activation patterns.

5. Is biased information processing measurable indirectly with a paradigm adapted from animal research and is a negative bias associated with depression related traits?

Hypothesis: Ambiguity with regard to a decision that is to be made shows in increased response times to these ambiguous, compared to non-ambiguous stimuli. Healthy individuals show a small positive bias in that they interpret ambiguous stimuli more often as having negative rather than positive consequences. However, the higher a person scores on depression-related traits, the more negative the bias will be. Ambiguity and the particular interpretation of a certain stimulus are also reflected in specific alterations of event-related potentials of the electroencephalogram. Ambiguous stimuli are expected to yield increased amplitudes of the N200 and of the late positive potential, while the interpretation of a stimulus as negative or positive should also affect the late positive potential amplitude.

4 Work program and methods

To address the questions raised in Chapter 3, six different studies were conducted, three testing for neural correlates of emotion regulation processes in affective disorders (see Section 5.1), two studies looked at the influence of emotion on cognitive processing in bipolar disorder (see Section 5.2) and one study investigated biased information processing (see Section 5.3).

Different populations were tested to investigate the neural correlates of emotional processing in depression and bipolar disorder and to specify potential impairments as vulnerability marker or consequence of bipolar disorder. The populations included healthy individuals to establish the respective paradigms and to serve as gender-, age- and education matched controls for the clinical groups and the groups at risk to develop bipolar disorder. Currently remitted patients with unipolar depression and euthymic patients with bipolar disorder type I were tested, as well as two populations at high risk to develop bipolar disorder. These were unaffected first-degree relatives of patients with bipolar disorder type I, who were unrelated, however, to the patients who participated in the studies, and healthy individuals with hypomanic personality. While relatives of bipolar patients are at risk because of their genetic heritage, individuals with hypomanic personality were identified by their scores in the Hypomanic Personality Scale (Eckblad & Chapman, 1986). In a 13 year longitudinal study participants scoring high in the Hypomanic Personality Scale showed greatly increased occurrence of bipolar disorder at follow-up (25% compared to 0% in the control group) (Kwapil et al., 2000). Thus, it is a method to psychometrically define increased risk for developing bipolar disorder. The two approaches to defining high risk to develop bipolar disorder therefore complement each other.

The outcome measures of the included studies were on the one hand behavioral responses to obtain indicators of performance speed and accuracy as well as subjective reports of experienced emotion and on the other hand functional magnetic resonance imaging (fMRI) and event-related potentials (ERP) of the electroencephalogram to allow conclusions about the neural correlates and timing of neural processes, respectively.

Functional MRI is a noninvasive method that is being used increasingly since its first description (Ogawa, Lee, Nayak, & Glynn, 1990; Turner, von Kienlin, Moonen, & van Zijl, 1990) because of its relatively high spatial resolution in the range of millimeters. It builds on neurovascular coupling, that is, neuronal activity in a certain region leads to increased flow of oxygenated blood into that region. Because

deoxyhemoglobin leads to greater signal loss in T2*-weighted MRI contrasts than oxygenated hemoglobin, currently active regions can be separated from currently inactive region, which is referred to as the blood oxygen level dependant response (BOLD). In comparison to the neural activity that causes it, BOLD is relatively slow and peaks around 6-8 seconds after the neural activity (this is also greatly variable depending, for example, on the specific region). Even though a number of studies showed a positive correlation of BOLD and neural activity (Lippert, Steudel, Ohl, Logothetis, & Kayser, 2010; Nair, 2005), fMRI results need to be interpreted with some care as fMRI does not measure neural activity directly and, furthermore, because all relations between neural activity and cognitive processes are purely correlational, not causal.

In the present work, two experimental strategies were used in fMRI. First an emotion regulation paradigm was developed, which combined previously applied emotion regulation tests by including a condition of cognitive change through reappraisal (Ochsner, Bunge, Gross, & Gabrieli, 2002) and an attentional control condition (Van Dillen et al., 2009). In the reappraisal condition, participants were instructed to re-evaluate a presented emotional image in order to reduce the elicited emotion. For example, when presented with an image of a crying child one could think that the child will be comforted soon and, in the long run, everything is going to be fine (Gross, 2002). In the attentional control condition, participants were also presented with emotional images, but solved arithmetic equations simultaneously (Van Dillen et al., 2009). Since the two emotion regulation strategies are psychologically very different, their joint investigation allows a better understanding of emotion regulation in affective disorders. The experimental details are described in the methods sections of the respective publications in Chapter 5 (Kanske, Heissler, Schonfelder, Bongers, & Wessa, 2011; Kanske, Heissler, Schonfelder, & Wessa, 2012; Kanske, Schonfelder, Forneck, & Wessa, in press).

Second, a two-step fMRI experiment was used to investigate the effects of emotion on cognitive processing. In a first step, the neural network involved in a specific cognitive task, a mental arithmetic task, was identified using an established procedure as a functional localizer (Rickard et al., 2000). In a second step, activity in this network was tested again with a mental arithmetic task, now with emotional and neutral distracters presented simultaneously. Thus, the effect of emotion on this network could be directly specified. Previous studies on emotional distraction effects did not include a functional localizer and could, therefore, not specify whether the observed effects were essential and specific to the task at hand, which may be the reason for the partly inconsistent findings of increased activity (Blair et al., 2007; Hart et al., 2010; Pereira et al., 2010) or decreased activity (Anticevic et al., 2010; Dolcos et al., 2006; Dolcos & McCarthy, 2006; Mitchell et al., 2008). Methodological details

are described in the methods sections of the publications in Chapter 5 (Kanske, Heissler, Schonfelder, Forneck, & Wessa, 2013; Wessa, Heissler, Schonfelder, & Kanske, 2013).

In contrast to fMRI, electroencephalography is an already old technique (Berger, 1929; Caton, 1875). It registers electrical fields from the scalp that are elicited by ionic currents in the brain (Gall et al., 2002). It is, therefore, a direct measure of neural activity and offers superior temporal resolution compared to fMRI. ERPs are voltage fluctuations of the electroencephalogram that are directly related to sensory, motor, affective, or higher cognitive events or processes and result from averaging time-locked epochs of the electroencephalogram, which cancels out noise and shows the activity that is due to such a specific event. Amplitude and latency differences of the components in the ERP are informative about the differences in the underlying processes and were used in the present work to study biased information processing in ambiguous situations.

The specific paradigm used in the ERP study was an adaptation of a task used in animals (Enkel et al., 2010; Harding et al., 2004). It presents two different tones, one always associated with a reward and the other with punishment. Participants need to press a button in order to actually obtain the reward or to avoid the punishment. After these associations are learned, additional tones are presented which are intermediate in frequency and, thus, ambiguous with regard to the potential consequence. Button presses to these ambiguous stimuli are taken as an indicator of a positive bias if the button to obtain reward is pressed more often and of a negative bias if the button to avoid punishment is pressed more often. In animals it had been shown that normal rats show a slight positive bias, while congenitally helpless rats, which were used as an animal model for depression, show a negative bias (Enkel et al., 2010). After enrichment, the negative bias of helpless rats shows a decrease, suggesting that the procedure might serve as a treatment outcome measure in depression as well (Richter et al., 2012). Beyond the potential for translational investigations of biased information processing, probing this particular paradigm also has the advantage that it is an indirect measure and does not build on previously established associations like previous investigations with affective prime sentences, naming latencies of valenced words, or sentence completions, which yielded overall incoherent results (Berna et al., 2011; Butler & Mathews, 1983; Lawson & MacLeod, 1999; Lawson et al., 2002). To establish this paradigm for use in affective disorder research we tested a group of healthy individuals and related the effects to inter-individual differences in depression related traits, such as rumination. For details of the experimental procedures see the methods section of the respective publication presented in Chapter 5 (Schick, Wessa, Vollmayr, Kuehner, & Kanske, 2013).

5 Experiments

5.1 Neural correlates of emotion regulation in healthy participants, remitted patients with depression, euthymic bipolar patients and unaffected relatives of bipolar patients

The section includes two published studies and a currently submitted study. The first study established a novel paradigm in healthy individuals that allows testing two different types of cognitive regulation of emotion, reappraisal (i.e. cognitively changing the emotional meaning of an event) and distraction (i.e. diverting attention away from an emotional event). The second and third study applied this paradigm to patients with remitted depression and euthymic bipolar patients and two groups at high risk to develop bipolar disorder.

- **Kanske, P.**, Heissler, J., Schönfelder, S., Bongers, A., Wessa, M. (2011). How to regulate emotion? Neural networks for reappraisal and distraction. *Cerebral Cortex, 21*, 1379-1388.
- **Kanske, P.**, Heissler, J., Schönfelder, S., Wessa, M. (2012). Neural correlates of emotion regulation deficits in remitted depression: The influence of regulation strategy, habitual regulation use, and emotional valence. *NeuroImage, 61*, 686-93.
- **Kanske, P.**, Schönfelder, S., Forneck, J., Wessa, M. (in press). Impaired regulation of emotion: Neural correlates of reappraisal and distraction in bipolar disorder and unaffected relatives. *Translational Psychiatry*.

Cerebral Cortex June 2011;21:1379–1388
doi:10.1093/cercor/bhq216
Advance Access publication November 1, 2010

How to Regulate Emotion? Neural Networks for Reappraisal and Distraction

Philipp Kanske[1], Janine Heissler[1,2], Sandra Schönfelder[1], André Bongers[3] and Michèle Wessa[1]

[1]Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, 68159 Mannheim, Germany, [2]Center for Doctoral Studies in Social and Behavioral Sciences, University of Mannheim, 68131 Mannheim, Germany and [3]Mediri GmbH, 69115 Mannheim, Germany

Address correspondence to Philipp Kanske, Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Square J5, 68159 Mannheim, Germany. Email: philipp.kanske@zi-mannheim.de.

The regulation of emotion is vital for adaptive behavior in a social environment. Different strategies may be adopted to achieve successful emotion regulation, ranging from attentional control (e.g., distraction) to cognitive change (e.g., reappraisal). However, there is only scarce evidence comparing the different regulation strategies with respect to their neural mechanisms and their effects on emotional experience. We, therefore, directly compared reappraisal and distraction in a functional magnetic resonance imaging study with emotional pictures. In the distraction condition participants performed an arithmetic task, while they reinterpreted the emotional situation during reappraisal to downregulate emotional intensity. Both strategies were successful in reducing subjective emotional state ratings and lowered activity in the bilateral amygdala. Direct contrasts, however, showed a stronger decrease in amygdala activity for distraction when compared with reappraisal. While both strategies relied on common control areas in the medial and dorsolateral prefrontal and inferior parietal cortex, the orbitofrontal cortex was selectively activated for reappraisal. In contrast, the dorsal anterior cingulate and large clusters in the parietal cortex were active in the distraction condition. Functional connectivity patterns of the amygdala activation confirmed the roles of these specific activations for the 2 emotion regulation strategies.

Keywords: affect, amygdala, fMRI, mental arithmetic, PPI

Introduction

Cognitively influencing emotional experience is highly relevant for adaptive social behavior and mental and physical health (Eftekhari et al. 2009). Different strategies can be applied to regulate emotional responses ranging from attentional control to cognitive change (Ochsner and Gross 2005). While attentional control enables the individual to focus away from an emotional stimulus (distraction), cognitive change yields an altered interpretation of an emotional situation (reappraisal). Both strategies have been shown to successfully modulate the subjective emotional state and activation in brain areas relevant for emotional processing including the amygdala (Kim and Hamann 2007; Van Dillen et al. 2009). However, we know little as to whether distraction and reappraisal differ in their effects on emotional experience and in the neural networks underlying the different regulation strategies (McRae et al. 2010). We, therefore, directly compared distraction and reappraisal using functional magnetic resonance imaging (fMRI).

Reappraisal is typically examined by instructing participants to alter their emotional response to images or other types of stimuli by reinterpreting their meaning (Ochsner et al. 2002; Eippert et al. 2007). It has been shown to reliably downregulate subjective emotional experience, psychophysiological indicators of emotion such as electrodermal activity and heart rate (Kalisch et al. 2005), and brain responses related to emotion as measured with electroencephalography (Hajcak et al. 2010) or fMRI (Urry et al. 2006; Kim and Hamann 2007; Kalisch 2009). Specifically, activation of the amygdala is reduced during reappraisal. Functional connectivity analyses showed that this reduction in amygdala activation during reappraisal is negatively related to activity in a neural network of control areas (Banks et al. 2007; Walter et al. 2009). A recent meta-analysis identified the dorsolateral and dorsomedial prefrontal cortex (dlPFC and dmPFC), the orbitofrontal cortex (OFC), and the parietal cortex (Kalisch 2009) as the most important nodes of this network.

Distraction, in contrast, relies on attentional control to focus on a concurrent task, thereby reducing emotional responding. A number of studies showed its efficiency in attenuating subjective emotional experience and amygdala activity (Pessoa et al. 2002; Blair et al. 2007; Erk et al. 2007; Van Dillen and Koole 2007). A recent study by Van Dillen et al. (2009) clearly demonstrated that amygdala downregulation is related to the difficulty of the concurrent task. More difficult tasks also engage areas in the dlPFC and superior parietal cortex that typically respond to task demands (de Fockert et al. 2001). The study provides some indication that activity in these control areas covaries with amygdala activation, but clear evidence for the connectivity of the amygdala during distraction is still lacking.

To data, the only study that aimed at comparing reappraisal and distraction combined reappraisal with a working memory task (McRae et al. 2010). They presented emotional pictures, and participants reinterpreted the images during reappraisal or kept a 6-letter string in memory during distraction. The authors reported activation of the dmPFC, dlPFC, and inferior parietal cortex for both tasks. Reappraisal yielded additional activations in the dmPFC and dlPFC, while distraction additionally activated the superior parietal cortex but also dlPFC. Interestingly, amygdala downregulation was stronger during distraction than reappraisal.

The present study aimed at further probing the 2 emotion regulation strategies to elucidate which parts of an emotion regulation network are common to reappraisal and distraction and which mechanisms are distinct to each strategy. Also, the reported data suggest similar, but not identical, effects of both strategies on emotional responses that we will test by contrasting reappraisal and distraction. A number of more specific questions remain: First, do the effects described by McRae et al. (2010) generalize to other distracting tasks? Here, it is also clinically relevant to show that easy, potentially self-generated tasks can regulate emotions. We, therefore, chose to

present arithmetic tasks in the distraction condition. Second, McRae et al. (2010) presented the regulation instructions prior to the emotional images. Thus, it is unclear if the effects differ for already elicited emotions. Again, this is clinically highly relevant as it is mainly fully developed emotional responses that need to be regulated in real-life situations. To address this, we included an emotion induction phase before the regulation instructions were presented. Third, in contrast to McRae et al., we included not only negative stimuli but also positive stimuli, as little is known about the effect of different emotion regulation strategies on emotional responses to negative and positive stimuli. And fourth, while we know that the amygdala is negatively coupled with prefrontal control regions during reappraisal (Urry et al. 2006; Banks et al. 2007), there is little evidence for the connectivity pattern during distraction and none directly comparing connectivity during the 2 regulation strategies. Therefore, we also compared functional connectivity of the amygdala during reappraisal and distraction.

To address these questions, we conducted an emotion regulation task where individuals were presented with neutral or emotional (negative and positive) images and, after a short emotion induction phase, passively viewed the images, reappraised their emotional meaning, or performed a simultaneously presented arithmetic task (distraction). We hypothesized that both active task conditions downregulate amygdala activity but that the neural networks subserving this regulation differ for reappraisal and distraction. Common network nodes should include regions in the dlPFC and dmPFC, as well as inferior parietal sites (McRae et al. 2010). In contrast, OFC activation should be observed for reappraisal only (Kalisch 2009), whereas distraction should yield activation specific to attentional control (e.g., dorsal anterior cingulate) and task-related activity in mainly superior parietal sites (Dehaene et al. 2004). Contrasting the connectivity patterns of the amygdala during reappraisal and distraction should corroborate these neural networks.

Materials and Methods

Participants

Thirty healthy volunteers (17 females, aged 18–27 years, mean age 21.8 ± 2.1 years) participated in the study. Twenty-six participants were right-handed, and 4 participants were left-handed according to the Edinburgh Handedness Inventory (Oldfield 1971). All participants had normal or corrected-to-normal vision and were medically healthy, reported no history of mental disorders as verified by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders IV (SCID-I and -II, First et al. 1997; German version, Wittchen et al. 1997), no history of serious head injury, or neurological disorder. The study was approved by the Ethics Committee of the University of Heidelberg, and all participants gave written informed consent prior to participation.

Experimental Paradigm and Procedure

The paradigm (Fig. 1) modifies and combines previous designs to study emotion regulation (Eippert et al. 2007; Van Dillen et al. 2009). Three task conditions were presented. In the view condition, participants attended the content of the picture but did not manipulate the emotional response to it. The distraction condition required participants to solve an arithmetic problem and to decide whether the displayed solution was correct or incorrect. The main focus of the reappraisal condition was to decrease any emotional response by reinterpreting the displayed situation, for example, as produced by actors and therefore not real, as meaning something else, or having a different outcome than initially suggested by the picture. Participants were also instructed to distance themselves from the image by reinterpreting the entire situation, for example, by reminding yourself that it is a photograph you are viewing, you are lying in a magnetic resonance scanner and are safe. To ensure that different results for reappraisal and distraction are not due to differences in task difficulty, a separate sample of 13 healthy volunteers performed the experimental task and rated the difficulty and effort required for each condition. These ratings were not significantly different (reappraisal $M = 5.1$, SD = 1.9; distraction $M = 4.6$, SD = 1.3; $F_{1,12} = 0.8$, $P > 0.35$).

Each trial started with a fixation cross presented with a jitter of 3000–5025 ms and followed by 1) an emotion induction phase, 2) the instruction and regulation phase (i.e., view, reappraisal, or distraction), and 3) a rating phase. During the induction phase (1000 ms), participants passively viewed a picture to elicit an initial emotional response. One of 3 instructions (view, decrease, or an arithmetic problem) was then presented for 1000 ms as a transparent overlay on the picture. The picture was presented for another 5000 ms. The arithmetic problem was continuously presented to allow for a solution of the problem. As soon as participants pressed a button to indicate whether the presented equation was correct or incorrect, a thin white frame line was presented around the arithmetic problem overlay. After picture presentation, participants rated their current emotional state on a 9-point scale using the Self-Assessment Manikins (SAM) ranging from unpleasant to pleasant (4000 ms).

Each picture was presented in the view, distraction, and reappraisal condition, except for the neutral images that were not presented for reappraisal. The experiment consisted of 128 trials, which were presented in a pseudorandomized order and lasted about 35 min. Participants received 6 training trials prior to the experiment, to familiarize them with the procedure and practice the emotion regulation strategies.

Stimuli

Pictures were selected from the International Affective Picture System (IAPS) based on normative ratings in valence and arousal (Lang et al. 2005). Sets of 16 negative, 16 neutral, and 16 positive stimuli were created (see Supplementary data 1 for a complete list of stimuli). Negative and positive stimuli were highly arousing, and neutral stimuli were rated low in arousal (see Table 1 for mean ratings). An analysis of variance (ANOVA) confirmed the selection, showing significant effects of picture category on valence and arousal ratings ($F_{2,45} = 1332.84$, $P < 0.001$ and $F_{2,45} = 176.65$, $P < 0.001$, respectively). Differences in valence ratings were observed for each category (all $P < 0.001$), while arousal ratings did not differ for positive versus negative but for emotional versus neutral stimuli ($P < 0.001$). The pictures were controlled for contents with all pictures (also neutral) displaying humans and for sex differences in valence and arousal ratings. Furthermore, differences in luminance and complexity were kept minimal. After the main experiment, all pictures were rated by the study participants on a 9-point scale using the Self-Assessment Manikins (see Table 1). The results were comparable to the normative IAPS ratings but differed in arousal ratings for the positive pictures, which were rated less arousing than negative pictures ($P < 0.001$).

All arithmetic problems were formed with 3 operands including a subtraction and an addition (e.g., 4 + 9 − 6 = 7). Participants were asked to solve the problems and decide whether the displayed solution was correct or incorrect. Initially, 130 arithmetic problems were tested in an independent sample of 10 healthy participants. From these, 48 equations were selected such that they were correctly solved by at least 75% of the sample. These selected equations were randomly assigned to the background picture condition (negative, neutral, or positive) such that there were no differences in reaction times or number of errors (all $P > 0.25$).

MRI Data Acquisition

MRI data were collected on a 3-T scanner (Magnetom TIM Trio; Siemens Medical Solutions) at the Central Institute of Mental Health, Mannheim, Germany. A high-resolution T_1-weighted 3D image was acquired (slice thickness = 1.1 mm, field of view (FOV) = 256 × 256 × 256 mm, matrix = 256 × 256 × 256). Functional images were obtained

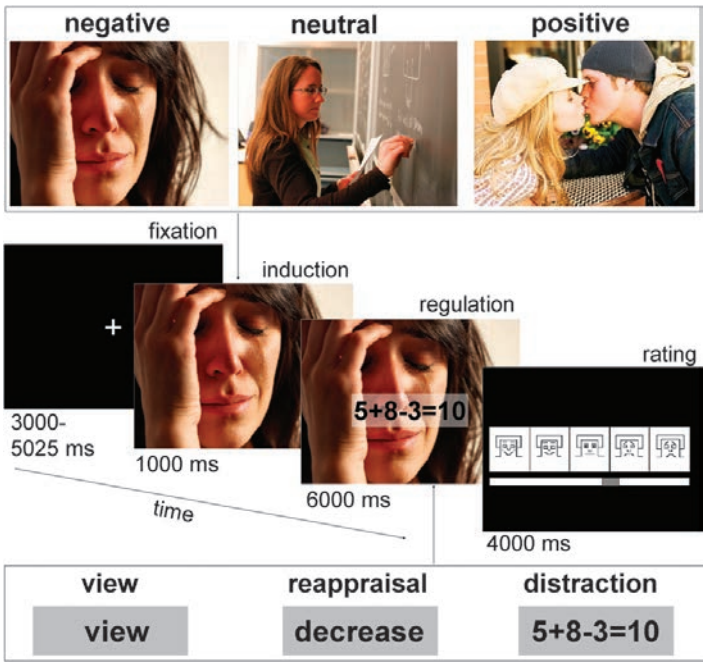


Figure 1. Sequence of events in a trial. The example pictures resemble those in the experiment but are not part of the IAPS.

Table 1
Mean valence and arousal ratings and standard deviations (in parentheses) for the picture selection

	Normative IAPS ratings		Sample ratings	
	Valence	Arousal	Valence	Arousal
Negative	1.87 (0.21)	6.28 (0.64)	2.48 (0.49)	6.00 (1.00)
Neutral	4.92 (0.28)	2.98 (0.34)	5.19 (0.42)	1.77 (0.35)
Positive	7.38 (0.39)	6.29 (0.68)	7.21 (0.35)	5.16 (0.60)

Note: Normative IAPS ratings and the ratings of the present sample are displayed.

from 40 gradient-echo T_2^*-weighted slices (slice thickness = 2.3 mm) per volume. A single-shot echo planar sequence with parallel imaging GRAPPA technique (acceleration factor 2) was used with a time repetition of 2700 ms, a flip angle of 90°, time echo = 27 ms, FOV = 220 × 220 mm, matrix = 96 × 96, and a slice gap of 0.7 mm.

fMRI Data Analysis

Image processing and statistical analysis was done with SPM5 (http://www.fil.ion.ucl.ac.uk/). Functional images were realigned, slice-time corrected, and spatially normalized using the Montreal Neurological Institute (MNI) template. For normalization, images were resampled every 3 mm using sinc interpolation. Images were smoothed using a 9 × 9 × 9-mm Gaussian kernel.

Analysis of Regional Brain Activations

Individual participants' data were analyzed using a General Linear Model for blood oxygen level–dependent (BOLD) signal changes due to the experimental conditions. Movement parameters calculated during realignment were included as parameters of no interest to control for movement artifacts. Individual statistical parametric maps were calculated for the following contrasts of interest in order to investigate BOLD signal changes: 1) for the initial emotional response during the induction phase (emotional vs. neutral pictures), 2) for the emotional response in the view condition (view emotional vs. view neutral conditions in the instruction phase), 3) for distraction (distraction emotional vs. view emotional in the instruction phase), and 4) for reappraisal (reappraisal emotional vs. view emotional in the instruction phase), and (5) to evaluate distinct neural correlates of distraction and reappraisal, we directly contrasted these 2 conditions (reappraisal emotional vs. distraction emotional in the instruction phase). In the first step, all analyses were done for positive and negative emotional stimuli separately, which yielded largely comparable results. Also, directly comparing the 2 emotional categories only yielded stronger activation for negative stimuli in the occipital cortex (see Supplementary data 2), which is not part of the emotion regulation networks. To enhance statistical power, we thus, pooled positive and negative stimuli, creating 1 emotional condition for the analyses reported here.

Two types of second-level random-effects analyses were conducted. First, 1-sample *t*-tests were calculated on the above-mentioned individual contrast images. Here, activations were thresholded at a whole-brain false discovery rate (FDR)-corrected $P < 0.01$ with an extent threshold of 20 voxels in order to protect against false-positive activations. Anatomically defined regions of interest (ROIs) from the automated anatomical labeling atlas in WFU PickAtlas v2.0 (Tzourio-Mazoyer et al. 2002) were used to examine amygdala activation (*P*-FDR < 0.05). Amygdala activations that were significant in the ROI analysis, but not in the whole-brain statistic, are marked in the results tables. Second, in order to evaluate common effects of distraction and reappraisal, we used the respective contrasts as inclusive masks and thresholded both contrasts at $P = 0.01$, yielding voxels whose probability of being activated randomly in both contrasts was $P < 0.001$ (according to the Fisher method for combining *P* values, see also Kampe et al. 2003).

Analysis of Functional Connectivity

To assess functional connectivity of the amygdala activation under reappraisal and distraction, we performed a psychophysiological

interaction (PPI) analysis as implemented in SPM5 (Friston et al. 1997). Our goal was to identify brain regions that have a downregulating effect on the amygdala, that is, regions showing an activation increase accompanied by an activation decrease in the amygdala. In the first step, a 5-mm spherical seed region around the peak activation in the anatomically defined amygdala ROI was identified for each participant when contrasting the combined reappraisal and distraction conditions with the view condition (reappraisal + distraction emotional vs. view emotional). Then, the deconvolved time series in the seed region (left amygdala) was extracted for each participant as the first regressor in the PPI analysis (physiological variable). The second regressor represented the experimental condition (reappraisal emotional vs. distraction emotional; psychological variable). The regressor of interest was the interaction between the time series of the seed region and the experimental condition (PPI). A negative correlation of this interaction term with activity in other brain regions indicates that an activation increase in these brain regions is related to a decrease in amygdala activity under reappraisal. In contrast, a positive correlation indicates that an activation increase in certain brain regions is associated with a decrease in amygdala activity under distraction. In the last step, the individual contrast images were entered into a second-level random-effects analysis, and 1-sample *t*-tests with a whole-brain FDR-corrected $P < 0.05$ were calculated.

For graphical display of the fMRI data, MRIcroN (http://www.cabiatl.com/mricro/index.html) was used with the MNI template brain.

Statistical Analyses of Behavioral Data

The emotional state ratings were analyzed with SPSS (version 15.0; SPSS Inc.). The first 1-way ANOVA was conducted to analyze the effect of the emotional picture presentation (negative, neutral, or positive) on emotional state in the viewing condition. A second 2 × 3 repeated-measures ANOVA including the factors emotion (negative or positive) and task (distraction, view, and reappraisal) was calculated to elucidate the effects of regulation on emotional state. The neutral condition was neglected for the second analysis as there were no neutral pictures in the reappraisal condition. All effects with a $P < 0.05$ were treated as statistically significant.

Results

Behavioral Data

Ratings

Analysis of the emotional state ratings after each trial (see Fig. 2) revealed a significant main effect of emotion in the viewing condition ($F_{2,58} = 165.3$, $P < 0.001$). Planned comparisons showed that negative and positive trials differed from neutral trials (negative vs. neutral: $F_{1,29} = 184.6$, $P < 0.001$; positive vs. neutral: $F_{1,29} = 95.4$, $P < 0.001$).

The second analysis regarding the regulation effects showed a significant main effect of emotion ($F_{1,29} = 113.8$, $P < 0.001$) and an interaction of emotion and task ($F_{2,58} = 105.5$, $P < 0.001$). Repeated contrasts regarding the interaction yielded significant effects (emotion × distraction-view: $F_{1,29} = 104.0$, $P < 0.001$; emotion × reappraisal-view: $F_{1,29} = 163.6$, $P < 0.001$), indicating that the emotional pictures were rated less negative or positive during distraction and reappraisal compared with the view condition. There was no main task effect ($F_{2,58} = 1.5$, $P > 0.20$).

fMRI Data

Induction Phase

To identify the regions involved in mere emotional processing of the stimuli, we analyzed, in the first step, activity for emotional versus neutral images in the preinstruction/emotion induction phase (see Table 2). Here, we observed activity bilaterally in the amygdala, insula, and in a large cluster in the ventromedial prefrontal cortex (vmPFC), including the subgenual anterior cingulate (sgACC). Furthermore, extensive activation in the occipital and more ventral temporal cortices and in the precuneus was observed for emotional pictures.

Main Effect of Emotion

In the second step, to identify the regions involved in emotional processing, we contrasted emotional and neutral pictures in the simple viewing condition (see Table 2). This analysis also yielded activation in the left amygdala, the left insula, and the vmPFC bilaterally, including the sgACC. Also, there was extensive activation in the occipital and ventral temporal cortices and in the posterior cingulate cortex.

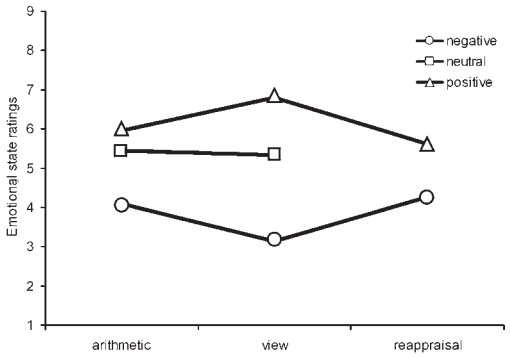


Figure 2. Emotional state ratings during the experiment. The means of SAM valence rating (1 = negative to 9 = positive) are displayed.

Table 2
Activations for emotional versus neutral pictures in the view condition

	H	BA	MNI coordinates			CS	CI	*T*
			x	*y*	*z*			
Induction phase: emotional–neutral								
Precuneus		7	0	−60	36		a	7.54
Temporal/occipital	L	37/19/18/17	48	−63	−6	10 604	**a**	9.91
	R	37/19/18/17	−51	−72	−3		a	8.59
Ventromedial frontal/anterior cingulate		25/10/11	0	24	−6		a	6.66
Insula	L	48	−48	9	0		a	3.83
	R	48	42	9	−6		a	4.01
Amygdala	L		−18	−3	−12		a	5.08
	R		18	−3	−15		a	3.44
Thalamus	R		6	−18	12		a	4.94
View emotional–view neutral								
Precuneus	L	19	−18	−81	48	26	**a**	3.95
	R	19	24	−81	48		b	5.08
Temporal/occipital	L	37/19/18/17	−48	−69	9		b	9.34
	R	37/19/18/17	48	−63	−3	3314	**b**	10.52
Ventromedial frontal/anterior cingulate	L	25/10/11	−3	27	−6	179	**c**	6.53
Posterior cingulate	L	31	−9	−51	27	240	**d**	6.15
Insula	L	48	−30	15	−15	32	**e**	6.41
Amygdala[a]	L		−18	−3	−12	14	**f**	2.98
Thalamus	L		−6	−18	6	134	**g**	4.88
	R		3	−9	6		g	4.45

Note: H, hemisphere; BA, Brodmann area; CS, cluster size in number of activated voxels; CI, cluster index; L, left; R, right; T-values for each peak are given: All peaks of 1 activation cluster are identified by the same letter; the cluster peaks are displayed in bold letters.
[a]ROI analysis.

Effects of Reappraisal

Activation in the bilateral amygdala and the vmPFC/sgACC was increased when comparing emotional pictures in the viewing condition to the reappraisal condition (see Table 3 and Fig. 3), indicating a reduction of activation in these areas through reappraisal. In contrast, reappraisal elicited enhanced activation in the OFC, the dlPFC, and the dmPFC. Other regions involved in reappraisal included the inferior parietal cortex, left middle temporal gyrus, and bilateral precuneus (see Fig. 4).

Table 3
Activations for reappraisal and distraction versus emotional pictures in the view condition

	H	BA	MNI coordinates			CS	CI	*T*
			x	*y*	*z*			
View emotional–reappraisal								
Postcentral	L	2/3	−39	−27	57	105	**a**	4.01
	R	2/3	51	−24	36	138	**b**	5.41
Temporal/occipital	L	37/19/18/17	−45	−78	−3		c	7.77
	R	37/19/18/17	48	−63	−6	4564	**c**	8.81
Ventromedial frontal/anterior cingulate	L	25/10/11	−3	30	−12	440	**d**	5.57
Posterior cingulate	R	30	12	−51	12	49	**e**	4.64
Insula	L	48	−42	−9	18	155	**f**	5.28
Amygdala	L		−21	−6	−18	69	**g**	4.65
	R		24	−3	−21		c	4.37
Caudate	L		−6	15	15		h	4.52
	R		3	18	12	49	**h**	5.02
Thalamus	L		−3	−15	6	51	**i**	4.29
	L		−21	−27	−3	33	**j**	4.22
Reappraisal–view emotional								
Superior/medial frontal	L	6/8	−12	12	63	270	**a**	6.23
	R	6/8	12	15	66		a	5.87
Middle frontal	L	6/9/46	−45	12	45	213	**b**	5.77
	R	6/9/46	39	36	42	128	**c**	6.5
	L	46	−30	45	12	28	**d**	4.87
	R	46	36	45	27	44	**e**	4.17
Orbitofrontal	L	47	−36	45	−3	119	**f**	5.42
	R	47	39	45	−9	84	**g**	7.94
Inferior parietal	L	39/40	−60	−51	33	416	**h**	7.86
	R	39/40	60	−54	39	343	**i**	8.19
Precuneus	L	7	−6	−69	36	90	**j**	5.58
	R	7	9	−66	36		i	3.89
Middle temporal	L	22	−54	−39	−3	214	**k**	6.32
Inferior temporal	L	20	−48	−3	−36	20	**l**	6.12
Middle cingulate	L	23	−6	−21	27	31	**m**	4.71
	R	23	6	−21	30		m	4.04
View emotional–distraction								
Superior medial frontal	L	8/9/10	−6	54	39	1046	**a**	10.39
Temporal/occipital	L	37/19	−51	−72	12	587	**b**	10.49
	R	37/19/18/17	45	−69	0	13 343	**c**	12.35
Ventromedial frontal/anterior cingulate	L	25/10/11	−3	48	−9	702	**d**	13.35
Insula	L	48	−33	−15	6		c	6.44
Amygdala	L		−21	−6	−21		c	9.72
	R		27	−3	−18		c	8.58
Distraction–view emotional								
Anterior cingulate/dorsomedial	L	6/8/32	−12	12	48		a	7.39
frontal	R	6/8/32	12	21	45		a	6.63
Middle frontal	L	6/44/45/46	−39	3	33		a	8.68
	R	9/44/45/46	45	33	27	342	**b**	7.53
Superior frontal	L	6/8	−21	6	57		a	7.02
	R	6/8	27	6	54		a	6.46
Superior parietal	L	7	−27	−63	45	6098	**a**	11.26
	R	7	33	−66	57		a	6.94
Inferior parietal	L	39/40	−45	−39	45		a	10.97
	R	39/40	45	−45	48		a	8.22
Precuneus	L	7	−12	−63	48		a	9.15
	R	7	9	−63	48		a	8.17
Inferior temporal	L	20/37	−54	−57	−12	85	**c**	5.68
Middle cingulate	L	23	−6	−24	27		a	8.09
	R	23	6	−24	27		a	7.62
Insula	L	48	−33	18	18		a	7.43
	R	48	33	21	0	97	**d**	7.83
Cerebellum	R		12	−78	−21	28	**e**	4.99

Note: H, hemisphere; BA, Brodmann area; CS, cluster size in number of activated voxels; CI, cluster index; L, left; R, right; T-values for each peak are given: All peaks of 1 activation cluster are identified by the same letter; the cluster peaks are displayed in bold letters.

Effects of Distraction

Similarly to reappraisal, activation in the bilateral amygdala and the vmPFC/sgACC was increased when comparing emotional pictures in the viewing condition to the distraction condition (see Table 3), here reflecting a reduction of activation in these areas through distraction. Distraction yielded enhanced activity in the dlPFC and the dmPFC, which included the dorsal ACC (dACC). Additionally, large clusters bilaterally in the parietal cortex, overlapping with and superior to the activation for reappraisal, were activated in the distraction condition. Further activity was observed in the bilateral insula (see Fig. 4). As the distraction condition differed from view and reappraisal in the continuous display of the overlay on the images, we compared emotional and neutral pictures in the distraction and view conditions to exclude the possibility that the overlay prevented perception and processing of the pictures. This analysis yielded conjunct activity in a number of areas including the insula (for details, see Supplementary data 3).

Common Effects of Reappraisal and Distraction

The analyses revealed 2 common effects of reappraisal and distraction: first, a downregulation of the amygdala and the vmPFC/sgACC for both regulation conditions as indicated by increased activity in these regions for the view condition as compared with distraction and reappraisal (see Fig. 3 and Table 4); second, overlapping activation increases for the 2 regulation strategies in the dmPFC and dlPFC, as well as in the precuneus and in the inferior parietal cortex (see Table 4).

Distinct Effects of Reappraisal and Distraction

To identify regions that were strongly engaged in one of the regulation strategies, we directly contrasted reappraisal and distraction, using inclusive masks of the respective main effects of each strategy (e.g., reappraisal-distraction was masked with reappraisal-view). This analysis showed that OFC activity was enhanced for reappraisal, while the dACC/dmPFC, large clusters in the parietal cortex, and the insula showed stronger activation for distraction (see Table 4). When repeating this analysis without the masks, we found the same pattern of activations and additionally a stronger reduction in activity in the bilateral amygdala and vmPFC/sgACC for distraction over reappraisal (see Table 4).

Functional Connectivity Analysis

To confirm the identified control networks for reappraisal and distraction, functional connectivity of the amygdala was calculated. To this end, amygdala connectivity in the 2 regulation conditions was directly contrasted (see Table 5). During reappraisal, an activation increase in a number of frontal areas including the OFC, as well as inferior parietal and middle temporal cortex was related to a decrease in amygdala activity. In contrast, an activation increase in the dACC/dmPFC, large clusters in the parietal cortex, as well as the right insula was associated with a decrease in amygdala activation in the distraction condition.

Discussion

The present study yielded several new insights into the neural correlates of emotion regulation. First, we could demonstrate

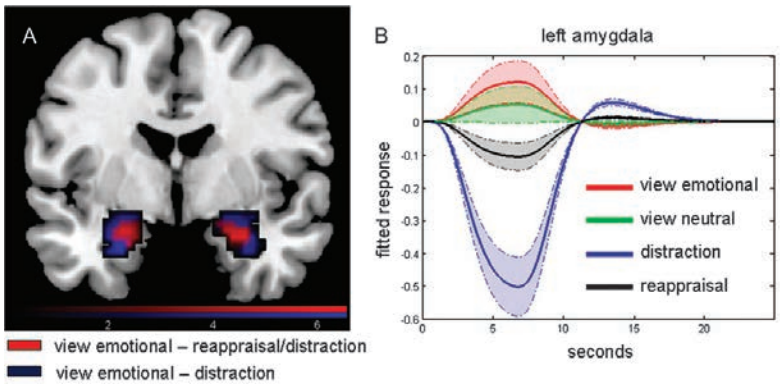


Figure 3. Reduction in amygdala activity (*A*) for the conjunction of reappraisal and distraction (in red, inclusive masking with $P < 0.01$ for each contrast, yielding a combined $P < 0.001$, see Methods) and the additional effect of distraction (in blue, exclusive masking with same thresholds). There was no additional effect of reappraisal. (*B*) Time-course of left amygdala activity for the different task conditions.

that 2 different regulation strategies, attentional control (distraction), and cognitive change (reappraisal) are effective in downregulating ongoing emotional responses to positive and negative stimuli on a neural and behavioral level. Second, this downregulation is subserved by a common network of control areas, including dlPFC, dmPFC, and parietal cortex. Third, both regulation strategies involve specific neural networks, which include the OFC for reappraisal and superior parietal sites, the dACC/dmPFC, and the insula for distraction. The role of these regulation networks was confirmed by functional connectivity of the left amygdala. Thereby the data extend recent findings from a study comparing reappraisal and a distracting memory task (McRae et al. 2010) showing that the effects generalize to different types of distraction, to emotions of different valence, to already elicited ongoing emotional responses, and to connectivity patterns of the distinct neural networks for reappraisal and distraction.

The 2 emotion regulation strategies investigated in the present study largely differ in their psychological mechanisms. While distraction relies on attentional control to shift the focus away from an emotional stimulus, for reappraisal, the focus remains on the emotional stimulus, but its meaning and personal relevance is reevaluated. Despite these differences, we found largely overlapping activations forming a common neural network underlying distraction and reappraisal including areas in the dlPFC, dmPFC, and inferior parietal cortex. These brain regions have been widely discussed for emotion regulation via reappraisal (Kalisch 2009) but also in the literature on attentional control (Egner and Hirsch 2005a, 2005b; Luks et al. 2007). Different types of conflict tasks such as Stroop or flanker paradigms as well as other executive control tasks reliably activate dlPFC, dmPFC, and parietal sites. Also the few studies that investigated emotion regulation through distraction from emotional stimuli yielded activation in these areas (Van Dillen et al. 2009; McRae et al. 2010). Therefore, both strategies draw on resources of a general cognitive control network that regulates the activity in brain areas denoted to the current task demands (e.g., fusiform face area in a face-word Stroop task, Egner and Hirsch 2005a; limbic regions in emotional interference tasks, Dillon et al. 2007) and thereby ensure coherent goal-directed behavior and efficient task performance.

Despite the described communalities of neural networks subserving reappraisal and distraction, we also found activity specific to each emotion regulation strategy. Bilaterally, the OFC was activated for reappraisal only and was also negatively coupled with left amygdala activity for reappraisal over distraction. OFC activation has been consistently reported in several reappraisal studies, both for down- and upregulation of an emotional response (e.g., Eippert et al. 2007). This regulating function of the OFC is in line with its involvement in affective reversal learning tasks (Kringelbach and Rolls 2003) as reappraisal can be described as a self-induced change in emotional responding during constant unchanged stimulation. Interestingly, patients with lesions in the OFC show deficits in the actualization of a current context (Schnider and Ptak 1999; Schnider 2003). In line with these data, the OFC is involved in distinguishing presently relevant from previously relevant information (Schnider et al. 2002). Reappraisal shares with these processes that the momentary relevance and meaning of a stimulus is changed. While the picture of a threatening event may be perceived as highly relevant and emotionally negative at first, its reappraisal as "just a picture taken in the past and presently irrelevant to me lying in the MR-Scanner" may render it neutral. The actualization of the present context and the reversal of the emotional meaning of a stimulus are specific to reappraisal, distinguish it from emotion regulation through attentional control, and rely on the OFC.

In contrast, the attentional control condition is characterized by orienting attention away from the emotional stimulus to a cognitive task, by the commitment of resources to the processing of this task, and by the detection of potential conflicts between task processing and emotional activation. Thereby attentional control secures the continuous dedication of resources to task processing. The dorsal portion of the anterior cingulate cortex has been widely discussed as a major node in the attentional control network, in particular for the monitoring of conflict between opposing activations (e.g., opposing response tendencies as in the Stroop task, see Botvinick et al. 2004). Interestingly, the activation of the dACC/dmPFC cluster in the present study was stronger in the distraction than the reappraisal condition. The PPI results also indicate enhanced negative coupling of the amygdala and the

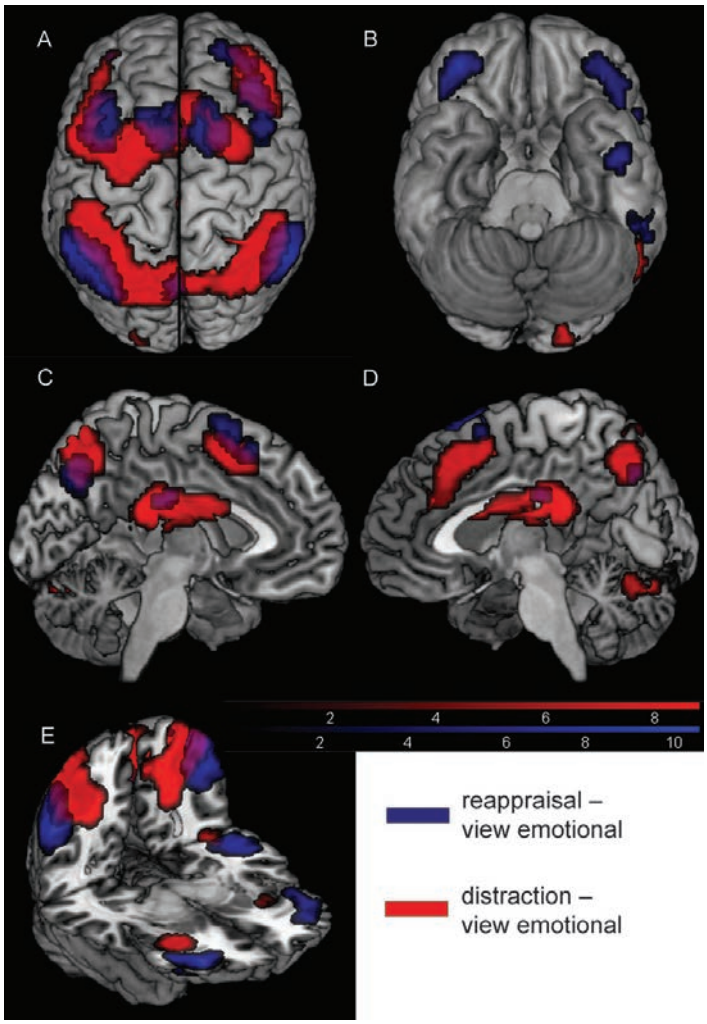


Figure 4. Activations for reappraisal (in blue) and distraction (in red) on the superior (*A*) and inferior (*B*) surface and on the opened (*E*) brain (cutting at $y = -52$ and $z = -5$). Medial effects are displayed for the left (*C*) and right (*D*) hemisphere ($x = -5$ and $x = 5$, respectively). All images are thresholded at whole-brain FDR-corrected $P < 0.01$ with an extent threshold of 20 voxels.

dACC/dmPFC for distraction, supporting the view that attentional control was particularly and more engaged in the distraction condition. We also found task-specific activations in the parietal cortex during distraction that nicely resembled previous data on mental arithmetic tasks in shape and location (Rickard et al. 2000; Fehr et al. 2007). Indeed, the processing of arithmetic problems largely involves different parts of the parietal cortex (intraparietal sulcus, inferior parietal lobule, angular gyrus, and superior parietal cortex; Menon et al. 2000; Dehaene et al. 2004; Grabner et al. 2009). Even though reappraisal also activated parts of the inferior parietal cortex, the activation elicited by distraction is larger, comprises additional areas in the superior parietal cortex, and its specific role for distraction is confirmed by the respective functional connectivity data. Distraction also yielded additional activation in the insula that was not observed for reappraisal. This is an interesting result as the insula has been mainly viewed as part of the emotional response network and is activated along with the amygdala and vmPFC/sgACC for emotional versus neutral pictures in the present study. However, the insula activation in the attentional control condition lies anterior to the emotional insula activity and can be clearly separated from it. This very anterior part of the insula has already been reported in other studies investigating mental arithmetics and is associated to task difficulty (Menon et al. 2000). Overall, the attentional control condition elicits specific activations additionally to the common regulation network that have been previously associated with executive attention (dACC) and that are

Table 4
Activations for reappraisal versus distraction and the results of the conjunction analysis

	H	BA	MNI coordinates			CS	CI	*T*
			x	*y*	*z*			
Reappraisal–distraction								
Superior medial frontal	L	6/8/9/10	−9	54	39	5324	**a**	9.97
Middle frontal	L	9	−39	15	45	76	**b**	5.22
Orbitofrontal	L	47	−48	30	−6		c	8.91
	R	47	36	39	−6	126	**d**	7.74
Inferior parietal	L	39/40	−45	−57	30	3195	**c**	8.94
	R	39/40	57	−63	36		a	8.01
Inferior temporal	L	20	−45	0	−33		c	8.54
	R	21	63	−12	−15	1127	**e**	8.37
Ventromedial frontal/anterior cingulate	L	25/10/11	−6	45	−9	555	**f**	7.14
Amygdala	L		−27	−6	−18		c	7.59
	R		30	−6	−27		e	6.33
Distraction–reappraisal								
Anterior cingulate/dorsomedial	L	6/8/32	−12	12	48		a	5.11
frontal	R	6/8/32	12	27	30		a	4.03
Superior frontal	L	6/8	−30	−3	54		a	5.94
	R	6/8	27	6	54		a	5.42
Superior parietal	L	7	−27	−60	45	4191	**a**	12.37
	R	7	30	−63	60		b	6.47
Inferior parietal	L	39/40	−48	−36	48		a	12.24
	R	39/40	45	−36	45	1035	**b**	8.6
Inferior temporal	L	20/37	−48	−60	−9	165	**c**	6.14
Insula	L	48	−30	21	−3		a	4.11
	R	48	33	21	0	67	**d**	5.24
Cerebellum	R		18	−54	−24	1183	**e**	7.64
Conjunction: reappraisal–distraction masked by reappraisal-view								
Superior medial frontal	L	6/8	−6	18	66	25	**a**	4.00
Middle frontal	L	9	−39	15	48	47	**b**	4.60
Orbitofrontal	L	47	−48	30	−12	61	**c**	7.58
	R	47	45	33	−6	33	**d**	6.41
Inferior parietal	L	39/40	−45	−57	27	193	**e**	5.69
	R	39/40	57	−60	24	235	**f**	6.26
Middle temporal	L	21	−63	−27	−6	186	**g**	5.22
Inferior temporal	L	20	−45	0	−36	23	**h**	6.90
Conjunction: distraction–reappraisal masked by distraction-view								
Anterior cingulate/dorsomedial	L	6/8/32	−12	12	48	790	**a**	3.12
frontal	R	6/8/32	9	30	33		a	3.02
Superior frontal	L	6/8	25	0	53		a	5.41
	R	6/8	25	9	54	121	**b**	4.60
Superior parietal	L	7	−28	−63	52		a	4.87
	R	7	30	−65	56		b	3.84
Inferior parietal	L	40	−42	−39	42	1235	**c**	7.82
	R	40	45	−42	51	609	**d**	6.53
Inferior temporal	L	20/37	−54	−57	−15	52	**e**	4.46
Insula	L	48	−33	18	9	58	**f**	4.11
	R	48	33	21	−5	53	**g**	3.88
Conjunction: view–reappraisal/distraction								
Middle temporal	L	37	−48	−72	12	31	**a**	3.79
	R	37	51	−60	6	123	**b**	7.55
Ventromedial frontal/anterior cingulate	L	25/10/11	−3	39	−12	373	**c**	10.03
Amygdala	L		−21	−6	−21	35	**d**	6.94
	R		24	−6	−21	223	**e**	6.07
Conjunction: reappraisal/distraction–view								
Dorsomedial frontal	L	6	−3	12	57	34	**a**	3.37
Middle frontal gyrus	L	46	−42	24	30	24	**b**	3.97
	L	6/9	−39	3	54	27	**c**	3.81
	R	9/46	39	45	30	61	**d**	3.7
Inferior parietal	L	40	−39	−54	45	114	**e**	5.44
	R	40	51	−45	51	54	**f**	4.59
Precuneus	L	7	−9	−63	45	39	**g**	6.25
	R	7	9	−66	42	27	**h**	5.07
Middle cingulate	R	23	3	−27	24	70	**i**	4.81

Note: H, hemisphere; BA, Brodmann area; CS, cluster size in number of activated voxels; CI, cluster index; L, left; R, right; T-values for each peak are given: All peaks of 1 activation cluster are identified by the same letter; the cluster peaks are displayed in bold letters.

specific to the present arithmetic task (broad parietal cluster) or are related to task difficulty (anterior insula). The functional role of these regions is corroborated by their increased negative coupling with the left amygdala for distraction over reappraisal.

Table 5
Results of the PPI analysis

	H	BA	MNI coordinates			CS	CI	*T*
			x	*y*	*z*			
PPI reappraisal								
Superior medial frontal	L	10	−6	63	15	63	**a**	3.59
		9	0	45	48	144	**b**	4.02
Superior frontal	R	6	21	−12	75	2764	**c**	4.76
Inferior orbitofrontal	L	47	−33	33	−12	20	**d**	3.83
	R	47	33	36	−12	25	**e**	4.31
Inferior parietal	R	39	54	−69	33	117	**f**	3.55
Middle temporal	L	20	−45	−9	−18	349	**g**	3.88
	R	22	63	−15	15	277	**h**	3.39
Ventromedial frontal/anterior cingulate	L	25/10/11	−9	27	−6	391	**i**	4.28
Amygdala	R		36	0	−18	185	**j**	4.89
PPI distraction								
Anterior cingulate/dorsomedial frontal	R	6/8/32	6	24	48	169	**a**	4.72
Middle frontal	L	44	−48	27	30	42	**b**	3.49
	L	6	−54	6	36	84	**c**	3.43
	R	44/46	48	30	36	50	**d**	3.82
Parietal	L	7/40	−42	39	45		e	4.68
	R	7/45	39	−45	45	79	**f**	3.63
Precuneus	L	7	−24	−60	42		e	3.53
	R	7	27	−60	45	99	**g**	3.51
Occipital	L	17/18/19	−24	−99	9	3359	**e**	7.46
Insula	R	47/48	36	24	−3	59	**h**	3.9

Note: H, hemisphere; BA, Brodmann area; CS, cluster size in number of activated voxels; CI, cluster index; L, left; R, right; T-values for each peak are given: All peaks of 1 activation cluster are identified by the same letter; the cluster peaks are displayed in bold letters.

As the neural networks for emotion regulation through attentional control and reappraisal are similar, so are the effects on behavioral and neural emotional responding. Emotional pictures reliably elicited an emotional response as could be seen in the online emotional state ratings and in activation in the amygdala, the vmPFC/sgACC, and the insula. These regions have been described as part of a ventral stream, which is supposed to be involved in the differentiation of emotional from nonemotional stimuli (Sabatinelli et al. 2009), emotional appraisal, and the production of an emotional state (Phillips et al. 2003; Stein et al. 2007). In line with previous studies, attentional control as well as cognitive change attenuated emotional responses (Goldin et al. 2008; Van Dillen et al. 2009). Subjective emotional state ratings as well as activity in the amygdala, vmPFC/sgACC, and the insula were lowered after reappraisal and distraction when compared with passive picture viewing. This corroborates recent data from McRae et al. (2010) and extends their findings to the regulation of both positive and negative emotions. Importantly, as the present experiment allows a direct comparison of the effects of reappraisal and distraction, we could also show a stronger and more extended reduction in amygdala activity in the distraction condition. This effect has to be interpreted with some care, as there was a continuous overlay on the images in the distraction condition, while the instruction overlay disappeared after 1 s during reappraisal and view. The overlay did not prevent participants from perceiving the images (see Supplementary data 3), but part of the reduction in amygdala activation could be due to the presence of this additional visual input. Nevertheless, the stronger effect for distraction is in line with other recent data (McRae et al. 2010). As described above, distraction differs from reappraisal in that it focuses attention away from the emotional content of a stimulus, while it is

necessary to focus on the emotional aspects of a stimulus in order to reappraise their meaning. This potentially leads to stronger activation in the ventral emotional stream for the reappraisal as compared with the distraction condition. Thus, as a short-term strategy for reducing an emotionally stressful response, distraction may prove to be an efficient intervention. This could also be relevant for psychotherapy in patients with difficulties in emotion regulation, for example in Borderline Personality Disorder or Bipolar Depression (Wessa et al. 2007; Gratz et al. 2009). Arithmetic tasks are particularly favorable in this regard as they are easy to implement and can be self-generated in emotionally stressful situations. It is also clinically relevant that the present study shows effects of reappraisal and distraction on ongoing emotional responses that have already been elicited (in contrast to McRae et al. (2010) who presented emotional stimuli after the regulation instruction), which is the primary challenge for patients in everyday situations. The present study did not address the duration of emotion regulation effects and future studies should elucidate the stability of the downregulating effects of reappraisal and distraction. The impact on long-term emotional responding may differ from the short-term effects reported here as memory for emotional stimuli is enhanced by reappraisal and impaired after distraction (Dillon et al. 2007; Sheppes and Meiran 2007). Furthermore, in a study comparing a distancing form of reappraisal to distraction during the recall of a depression experience, Kross and Ayduk (2008) showed that reappraisal protected against depressive affect 1 and 7 days after the experiment. Distraction and reappraisal may, therefore, differ in their long- and short-term effects, raising the important clinical question if different emotion regulation strategies should be taught with respect to specific situations and goals in psychotherapy (e.g., reduce present anger or long-term depressive feelings).

Despite the strong and consistent results of BOLD response changes and subjective emotional state changes during reappraisal and distraction, the interpretation of our results are limited by the lack of additional measures, such as eye movement patterns (van Reekum et al. 2007) as well as physiological indicators of emotional responsivity (e.g., electrodermal activity, heart rate). These indicators are highly correlated to subjective evaluation of emotional state (Cuthbert et al. 1996) and to the downregulation of anxiety (Kalisch et al. 2005) but not necessarily to the emotion regulation per se (Eippert et al. 2007). Whether these measures are sensitive to the different regulation strategies and which mechanisms of emotion regulation are reflected by the physiological indicators remain unclear and should be investigated in future studies.

To conclude, we confirmed and extend recent findings on neural correlates of reappraisal and distraction (McRae et al. 2010) showing that these different emotion regulation strategies are effective in downregulating ongoing subjective and physiological responses to emotional stimuli of different valence. The combination of 2 emotion-regulation strategies allowed us to identify a common neural control network in dlPFC, dmPFC, and inferior parietal cortex and to additionally show distinct strategy-specific activations in the OFC for reappraisal and the dACC, parietal cortex, and insula for attentional control (distraction). Moreover, an important and new insight from the present study was that these strategy-specific activations showed increased negative coupling with the left amygdala when reappraisal and distraction were compared. Emotional state ratings and downregulation of the initially elicited amygdala activation indicated robust effects of both strategies on emotional responding.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

Funding

Deutsche Forschungsgemeinschaft (We3638/3-1).

Notes

We wish to thank Heike Schmidt for help with the data acquisition. *Conflict of Interest*: None declared.

References

Banks SJ, Eddy KT, Angstadt M, Nathan PJ, Phan KL. 2007. Amygdala-frontal connectivity during emotion regulation. Soc Cogn Affect Neurosci. 2:303–312.

Blair KS, Smith BW, Mitchell DG, Morton J, Vythilingam M, Pessoa L, Fridberg D, Zametkin A, Sturman D, Nelson EE, et al. 2007. Modulation of emotion by cognition and cognition by emotion. Neuroimage. 35:430–440.

Botvinick MM, Cohen JD, Carter CS. 2004. Conflict monitoring and anterior cingulate cortex: an update. Trends Cogn Sci. 8:539–546.

Cuthbert BN, Bradley MM, Lang PJ. 1996. Probing picture perception: activation and emotion. Psychophysiology. 33:103–111.

de Fockert JW, Rees G, Frith CD, Lavie N. 2001. The role of working memory in visual selective attention. Science. 291:1803–1806.

Dehaene S, Molko N, Cohen L, Wilson AJ. 2004. Arithmetic and the brain. Curr Opin Neurobiol. 14:218–224.

Dillon DG, Ritchey M, Johnson BD, LaBar KS. 2007. Dissociable effects of conscious emotion regulation strategies on explicit and implicit memory. Emotion. 7:354–365.

Eftekhari A, Zoellner LA, Vigil SA. 2009. Patterns of emotion regulation and psychopathology. Anxiety Stress Coping. 22:571–586.

Egner T, Hirsch J. 2005a. Cognitive control mechanisms resolve conflict through cortical amplification of task-relevant information. Nat Neurosci. 8:1784–1790.

Egner T, Hirsch J. 2005b. The neural correlates and functional integration of cognitive control in a Stroop task. Neuroimage. 24:539–547.

Eippert F, Veit R, Weiskopf N, Erb M, Birbaumer N, Anders S. 2007. Regulation of emotional responses elicited by threat-related stimuli. Hum Brain Mapp. 28:409–423.

Erk S, Kleczar A, Walter H. 2007. Valence-specific regulation effects in a working memory task with emotional context. Neuroimage. 37:623–632.

Fehr T, Code C, Herrmann M. 2007. Common brain regions underlying different arithmetic operations as revealed by conjunct fMRI-BOLD activation. Brain Res. 1172:93–102.

First MB, Gibbon M, Spitzer RL, Williams JBW. 1997. Structured clinical interview for DSM IV axis I disorders (SCID-I). Arlington (TX): American Psychiatric Publishing, Inc.

Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ. 1997. Psychophysiological and modulatory interactions in neuroimaging. Neuroimage. 6:218–229.

Goldin PR, McRae K, Ramel W, Gross JJ. 2008. The neural bases of emotion regulation: reappraisal and suppression of negative emotion. Biol Psychiatry. 63:577–586.

Grabner RH, Ansari D, Koschutnig K, Reishofer G, Ebner F, Neuper C. 2009. To retrieve or to calculate? Left angular gyrus mediates the retrieval of arithmetic facts during problem solving. Neuropsychologia. 47:604–608.

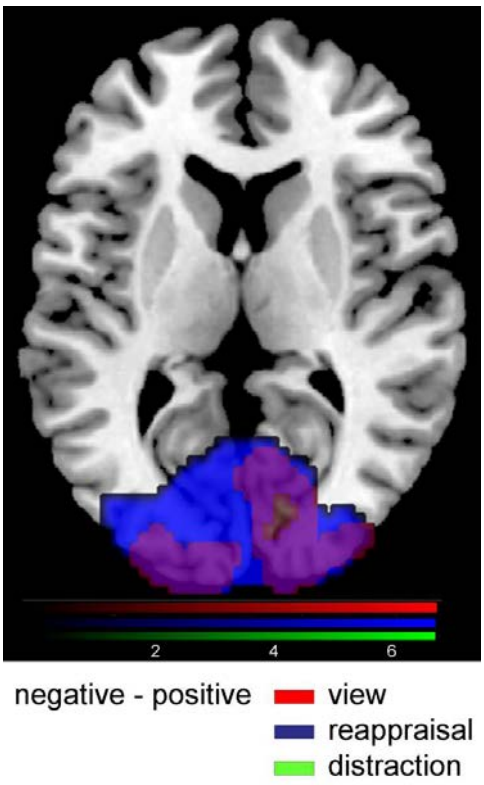
Gratz KL, Tull MT, Reynolds EK, Bagge CL, Latzman RD, Daughters SB, Lejuez CW. 2009. Extending extant models of the pathogenesis of borderline personality disorder to childhood borderline personality

symptoms: the roles of affective dysfunction, disinhibition, and self- and emotion-regulation deficits. Dev Psychopathol. 21:1263–1291.
Hajcak G, MacNamara A, Olvet DM. 2010. Event-related potentials, emotion, and emotion regulation: an integrative review. Dev Neuropsychol. 35:129–155.
Kalisch R. 2009. The functional neuroanatomy of reappraisal: time matters. Neurosci Biobehav Rev. 33:1215–1226.
Kalisch R, Wiech K, Critchley HD, Seymour B, O'Doherty JP, Oakley DA, Allen P, Dolan RJ. 2005. Anxiety reduction through detachment: subjective, physiological, and neural effects. J Cogn Neurosci. 17:874–883.
Kampe KK, Frith CD, Frith U. 2003. "Hey John": signals conveying communicative intention toward the self activate brain regions associated with "mentalizing," regardless of modality. J Neurosci. 23:5258–5263.
Kim SH, Hamann S. 2007. Neural correlates of positive and negative emotion regulation. J Cogn Neurosci. 19:776–798.
Kringelbach ML, Rolls ET. 2003. Neural correlates of rapid reversal learning in a simple model of human social interaction. Neuroimage. 20:1371–1383.
Kross E, Ayduk O. 2008. Facilitating adaptive emotional analysis: distinguishing distanced-analysis of depressive experiences from immersed-analysis and distraction. Pers Soc Psychol Bull. 34: 924–938.
Lang PJ, Bradley MM, Cuthbert BN. 2005. International affective picture system (IAPS): affective ratings of pictures and instruction manual. Technical report A-6. Gainesville (FL): Center for Research in Psychophysiology, University of Florida.
Luks TL, Simpson GV, Dale CL, Hough MG. 2007. Preparatory allocation of attention and adjustments in conflict processing. Neuroimage. 35:949–958.
McRae K, Hughes B, Chopra S, Gabrieli JD, Gross JJ, Ochsner KN. 2010. The neural bases of distraction and reappraisal. J Cogn Neurosci. 22:248–262.
Menon V, Rivera SM, White CD, Glover GH, Reiss AL. 2000. Dissociating prefrontal and parietal cortex activation during arithmetic processing. Neuroimage. 12:357–365.
Ochsner KN, Bunge SA, Gross JJ, Gabrieli JD. 2002. Rethinking feelings: an FMRI study of the cognitive regulation of emotion. J Cogn Neurosci. 14:1215–1229.
Ochsner KN, Gross JJ. 2005. The cognitive control of emotion. Trends Cogn Sci. 9:242–249.
Oldfield RC. 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia. 9:97–113.
Pessoa L, McKenna M, Gutierrez E, Ungerleider LG. 2002. Neural processing of emotional faces requires attention. Proc Natl Acad Sci U S A. 99:11458–11463.
Phillips ML, Drevets WC, Rauch SL, Lane R. 2003. Neurobiology of emotion perception I: the neural basis of normal emotion perception. Biol Psychiatry. 54:504–514.
Rickard TC, Romero SG, Basso G, Wharton C, Flitman S, Grafman J. 2000. The calculating brain: an fMRI study. Neuropsychologia. 38:325–335.
Sabatinelli D, Lang PJ, Bradley MM, Costa VD, Keil A. 2009. The timing of emotional discrimination in human amygdala and ventral visual cortex. J Neurosci. 29:14864–14868.
Schnider A. 2003. Spontaneous confabulation and the adaptation of thought to ongoing reality. Nat Rev Neurosci. 4:662–671.
Schnider A, Ptak R. 1999. Spontaneous confabulators fail to suppress currently irrelevant memory traces. Nat Neurosci. 2:677–681.
Schnider A, Valenza N, Morand S, Michel CM. 2002. Early cortical distinction between memories that pertain to ongoing reality and memories that don't. Cereb Cortex. 12:54–61.
Sheppes G, Meiran N. 2007. Better late than never? On the dynamics of online regulation of sadness using distraction and cognitive reappraisal. Pers Soc Psychol Bull. 33:1518–1532.
Stein JL, Wiedholz LM, Bassett DS, Weinberger DR, Zink CF, Mattay VS, Meyer-Lindenberg A. 2007. A validated network of effective amygdala connectivity. Neuroimage. 36:736–745.
Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage. 15:273–289.
Urry HL, van Reekum CM, Johnstone T, Kalin NH, Thurow ME, Schaefer HS, Jackson CA, Frye CJ, Greischar LL, Alexander AL, et al. 2006. Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. J Neurosci. 26:4415–4425.
Van Dillen LF, Heslenfeld DJ, Koole SL. 2009. Tuning down the emotional brain: an fMRI study of the effects of cognitive load on the processing of affective images. Neuroimage. 45:1212–1219.
Van Dillen LF, Koole SL. 2007. Clearing the mind: a working memory model of distraction from negative mood. Emotion. 7:715–723.
van Reekum CM, Johnstone T, Urry HL, Thurow ME, Schaefer HS, Alexander AL, Davidson RJ. 2007. Gaze fixations predict brain activation during the voluntary regulation of picture-induced negative affect. Neuroimage. 36:1041–1055.
Walter H, von Kalckreuth A, Schardt D, Stephan A, Goschke T, Erk S. 2009. The temporal dynamics of voluntary emotion regulation. PLoS One. 4:e6726.
Wessa M, Houenou J, Paillere-Martinot ML, Berthoz S, Artiges E, Leboyer M, Martinot JL. 2007. Fronto-striatal overactivation in euthymic bipolar patients during an emotional go/nogo task. Am J Psychiatry. 164:638–646.
Wittchen H-U, Zaudig M, Fydrich T. 1997. SKID-I. Strukturiertes Klinisches Interview für DSM-IV [Structural clinical interview for DSM-IV axis I disorders]. Göttingen (Germany): Hogrefe.

Supplement 1

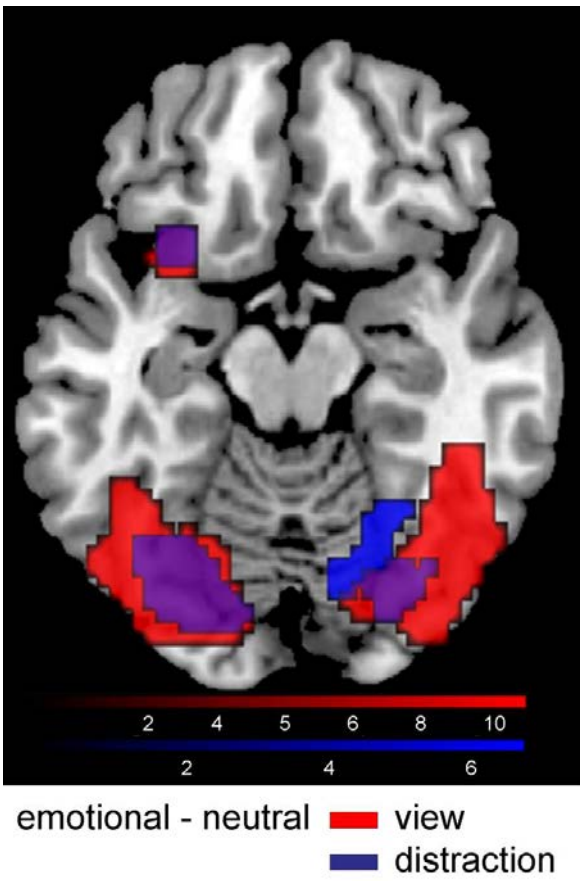
Description	IAPS number
negative	
SadChildren	2703
SadChild	2800
Mutilation	3010
Accident	3015
Mutilation	3060
Mutilation	3080
Infant	3350
Soldier	6212
DeadBody	9252
Mutilation	9253
Assault	9254
Soldier	9410
ManOnFire	9635,1
CarAccident	9910
Fire	9921
DyingMan	3230
neutral	
NeuMan	2102
Man	2190
NeutMan	2215
Secretary	2383
Factoryworker	2393
Couple	2396
Men	2397
NeutGirl	2440
ElderlyMan	2480
Man	2495
Man	2570
Shopping	2745,1
Chess	2840
Teenager	2870
Man	7493
Rain	9210
positive	
Boys	2224
Family	2340
EroticCouple	4608
Wedding	4626
EroticCouple	4660
EroticCouple	4687
EroticCouple	4689
EroticCouple	4695
SkyDivers	5621
Hiker	5629
Skier	8030
Skier	8190
WaterSkier	8200
Rafting	8370
Athletes	8380
RollerCoaster	8490

Supplement 2



Regions in the occipital cortex activated for negative compared to positive stimuli in the view, reappraisal, and distraction conditions.

Supplement 3



While the instruction overlay on the images disappeared after 1 s in the reappraisal and view conditions, it was continuously presented in the distraction condition. To exclude the possibility that the overlay prevented perception and processing of the contents of the images, two analyses were performed. First, while the ratings of current emotionality were reduced in the distraction (and reappraisal) condition compared to view, they were still significantly different in the distraction-emotional compared to the distraction-neutral condition (negative vs. neutral: $F(1,29) = 80.5$, $p < .001$; positive vs. neutral: $F(1,29) = 26.0$, $p < .001$). Second, we compared activations for emotional vs. neutral pictures in the distraction and the view condition. Here, overlapping activations would also indicate that the emotional content of the images was perceived. We found significant overlap between the conditions in several regions including the bilateral insula, occipital cortex and ventral temporal areas (see Figure and Table). These results were confirmed in a conjunction analysis of the two contrasts (with the same thresholds as in the other conjunctions described in the manuscript). These results suggest that the continuous display of the overlay in the distraction condition did not prevent participants from perceiving and processing the emotional images.

Table: Activations for emotional vs. neutral pictures in the view condition.

	H	BA	MNI coordinates			Cs	Cl	T
			x	y	z			
distraction: emotional - neutral								
insula	L	48	-30	15	-15	25	**a**	4.62
temporal/occipital	L	37/19/18/17	9	-75	-3	2977	**b**	7.64
	R	37/19/18/17	-42	-81	12		b	7.40
superior medial frontal	L	9	-24	54	24	23	c	4.07
	R	10	9	63	24	312	**c**	5.18
conjunction: distraction emotional - neutral masked by view emotional – neutral								
insula	L	48	-40	12	3	350	**a**	4.16
	R	48	39	9	-3	67	**b**	3.53
temporal/occipital	L	37/19/18/17	-9	-90	-6		b	10.01
	R	37/19/18/17	30	-84	-15	8391	**c**	10.36

H = Hemisphere; BA = Brodmann Area; CS = Cluster size in number of activated voxels; CI = Cluster index: all peaks of one activation cluster are identified by the same letter, the cluster peaks are displayed in bold letters.

NeuroImage 61 (2012) 686–693

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Neural correlates of emotion regulation deficits in remitted depression: The influence of regulation strategy, habitual regulation use, and emotional valence

Philipp Kanske [a,b,*], Janine Heissler [b,c], Sandra Schönfelder [a,b], Michèle Wessa [a,b]

[a] Section for Experimental Psychopathology and Neuroimaging, Department of General Psychiatry, Center for Psychosocial Medicine, Heidelberg University, Germany
[b] Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany
[c] Center for Doctoral Studies in Social and Behavioral Sciences, Graduate School of Economic and Social Sciences, University of Mannheim, Germany

ARTICLE INFO

Article history:
Accepted 30 March 2012
Available online 10 April 2012

Keywords:
Affect
Amygdala
Orbitofrontal cortex
Anterior cingulate cortex
fMRI
Reappraisal

ABSTRACT

Regulating emotions through reappraisal has been shown to elicit abnormal neural activation patterns in currently depressed patients. It is, however, unclear if this deficit generalizes to other emotion regulation strategies, if it persists when patients recover, and if it is related to habitual use of reappraisal strategies. Therefore, we measured the neural responses to emotional images with functional magnetic resonance imaging in remitted patients with previous episodes of major depression and healthy controls. While viewing the images participants regulated the elicited emotions using either a reappraisal or a distraction strategy. Habitual reappraisal use was measured with the Cognitive Emotion Regulation Questionnaire. Depressed patients showed a selective deficit in down-regulating amygdala responses to negative emotional stimuli using reappraisal. This down-regulation of amygdala activity was strongest in participants high in habitual reappraisal use. Activity in the regulating control-network including anterior cingulate and lateral orbitofrontal cortex was increased during both emotion regulation strategies. The findings in remitted patients with previous episodes of major depression suggest that altered emotion regulation is a trait-marker for depression. This interpretation is supported by the relation of habitual reappraisal use to amygdala down-regulation success.

Introduction

Altered affective processing is one of the defining characteristics of major depressive disorder (MDD). Its neural signature includes hyperactivity in a number of brain structures involved in emotion detection and generation (Drevets et al., 2002; Sheline et al., 2001). A critical question is whether the altered emotional responsivity in MDD is mirrored by impaired regulation of emotion. In contrast to a relatively large number of studies on automatic emotion regulation as assessed with simple emotion viewing paradigms (Dannlowski et al., 2009; Ritchey et al., 2011), there is only little evidence regarding the non-automatic cognitive control of emotions tested through explicit instructions to regulate current affect. The few data on cognitive control of emotions suggest a deficit in the capability to down-regulate amygdala activity to negative emotional stimuli (Beauregard et al., 2006), and altered connectivity between the amygdala and prefrontal control regions (Erk et al., 2010; Johnstone et al., 2007). Four major questions arise from these studies.

First, the specific cognitive regulation strategy that previous studies applied was reappraisal, which requires participants to reinterpret the meaning of emotional stimuli yielding them less negative and arousing (Gross, 2001). It is unclear, however, if the deficit in cognitive emotion regulation is restricted to reappraisal or generalizes to other emotion regulation strategies. Recent evidence in healthy participants demonstrated that reappraisal and an attentional control strategy (distraction) recruit overlapping, but distinct neural networks. While both strategies activated dorsolateral prefrontal (dlPFC) and parietal cortices, orbitofrontal cortex (OFC) activation was specific to using reappraisal, while distraction yielded more extensive activation in parietal and dorsomedial prefrontal/anterior cingulate cortex (dmPFC, ACC; Kanske et al., 2011; McRae et al., 2010). The tested strategies also differed in their effectiveness in amygdala down-regulation, with distraction yielding stronger and more extended down-regulation of the amygdala activity. The specific networks involved in emotion regulation have been shown to be differentially affected in depression. Lateral parts of the OFC show hyperactivation (Drevets, 2007), while for dorsal ACC and dlPFC, hyper- as well as hypoactivation have been reported (Disner et al., 2011; Wagner et al., 2006). Increased activation in control regions has been interpreted as a compensatory mechanism, which might also apply for emotion regulation in depression (Wagner et al., 2006). Furthermore, a recent meta-analysis showed structural changes in depression to be located more consistently in the OFC (Arnone et al., 2012). We, therefore, asked if emotion regulation deficits in depressed patients might differ between strategies.

* Corresponding author at: Section for Experimental Psychopathology and Neuroimaging, Department of General Psychiatry, Center for Psychosocial Medicine, University Clinic Heidelberg, Germany. Fax: +49 6221 56 5374.
E-mail address: philipp.kanske@med.uni-heidelberg.de (P. Kanske).

1053-8119/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2012.03.089

Second, as previous studies investigated emotion regulation in currently depressed but not remitted patients (Beauregard et al., 2006; Erk et al., 2010; Johnstone et al., 2007), we do not know if the deficit persists when patients recover. Because of high relapse rates (Hardeveld et al., 2010), remission is a vulnerable clinical state also characterized by greater sensitivity to mood challenges that predict recurrence (Segal et al., 1999) and related changes in orbitofrontal and cingulate activation patterns (Liotti et al., 2002). It remains to be investigated if altered regulation of emotion also reflects a trait-marker for depression and is not necessarily linked to present symptoms.

Third, it has been shown that depression is related to habitual differences in the use of emotion regulation through reappraisal. A recent meta-analysis, for example, reported reduced reappraisal use in depression (Aldao et al., 2010). Interestingly, habitual reappraisal use is also related to incremented emotional responding in currently remitted patients (Joormann and Gotlib, 2010). Nevertheless, it still needs to be tested if these habitual differences are related to impaired amygdala regulation during reappraisal use in neuroimaging experiments.

Fourth, previous studies concentrated on the down-regulation of negative emotion (Beauregard et al., 2006; Erk et al., 2010; Johnstone et al., 2007), which may be suggestive because of the excess of negative emotion in depression. Nevertheless, it is unclear if the deficit is selective to negative emotion or generalizes to positive emotion as well.

To address these questions, we examined two different cognitive emotion regulation strategies, reappraisal and distraction, in patients with previous depressive episodes currently in remission. While reappraisal is a form of cognitive change of emotion, distraction requires attentional control to divert attention to the performance of a parallel task, reducing the resources available for emotional processing (Ochsner and Gross, 2005). To differentiate the control of negative and positive emotion we used pictures of different valence and measured neural responses while patients applied emotion regulation with functional magnetic resonance imaging (fMRI). We also assessed habitual differences in the use of reappraisal using a validated questionnaire (Garnefski and Kraaij, 2007). This allowed testing four major hypotheses. First, if the deficits in regulating emotions are specific to the reappraisal strategy, than application of the distraction strategy should not yield any differences between healthy participants and MDD patients. Candidate regions for alterations include the amygdala as the major site for regulation effects, and the OFC and ACC/dmPFC as part of the control networks for reappraisal and distraction, respectively. In the amygdala we expect impairments to show in reduced down-regulation of activity in depression. In contrast, in line with the concept of compensatory hyperactivation, patients should show an activation increase in control regions. Second, if emotion regulation deficits are a trait-marker for depression we expect to also observe this in remitted MDD patients. Third, we expect to find a relation of neural activation changes during emotion regulation to habitual use of emotion regulation. Fourth, as depression is mainly characterized by excessive negative emotion, the deficits should be specific to down-regulating negative, but not positive emotion.

Table 1
Demographic and clinical characteristics for patients with major depressive disorder (MDD) and healthy control participants (HC).

	HC	MDD	Statistics	p-value
	n = 25	n = 23		
Gender ratio (female/male)	18/7	16/7	$Chi^2(1) = .034$	p = .853
Age. Mean (SD)	43.88 (11.21)	43.65 (10.12)	t(46) = −.074	p = .942
Years of education. Mean (SD)	11.40 (1.66)	11.39 (1.85)	t(46) = −.017	p = .986
Intelligence score. Mean (SD)	107.92 (15.27)	106.65 (15.32)	t(46) = −.287	p = .775
% married lifetime	68	69.6	$Chi^2(1) = .009$	p = .924
% currently employed	96	69.9	$Chi^2(1) = 6.027$	p = .014*
Handedness: LQ-Scores. mean (SD)	83.03 (25.79)	68.99 (50.19)	t(46) = −1.203	p = .238
Current symptoms				
HAMD. Mean (SD)	.04 (.20)	.91 (1.38)	t(46) = 3.008	p = .006**
ADS. Mean (SD)	4.50 (4.10)	12.26 (8.58)	t(45) = 3.931	p < .001**
BDI. Mean (SD)	.96 (1.46)	6.26 (6.14)	t(46) = 4.035	p < .001**
BDI. Affective subscale. Mean (SD)	.36 (.907)	3.17 (3.97)	t(46) = 3.318	p = .003**
BDI. Somatic subscale. Mean (SD)	.60 (1.00)	3.09 (2.84)	t(46) = 3.975	p < .001**
Substances				
Current medication [subjects (n); duration (months). mean (SD)]				
Antidepressant — SSRI	–	3; 61.33 (49.98)	–	–
Antidepressant — SSNRI	–	3; 29.67 (18.01)	–	–
Antidepressant — tricyclic	–	1; 131	–	–
Lithium	–	4; 88.75 (36.13)	–	–
Anticonvulsants	–	3; 73.5 (44.7)	–	–
Atypical antipsychotics	–	4; 47 (16.75)	–	–
None	25	14	–	–
Medication load. mean (SD) #	0	2.48 (2.26)	–	–
Persons regularly consuming caffeine. No. (%)	18 (72)	18 (78.3)	$Chi^2(1) = .629$	p = .428
Persons regularly consuming nicotine. No. (%)	4 (16)	2 (8.7)	$Chi^2(1) = .584$	p = .445
Persons regularly consuming alcohol. No. (%)	7 (28)	7 (30.4)	$Chi^2(1) = .034$	p = .853
Clinical characteristics				
Age at onset of disease. Mean (SD) age	–	32.09 (11.56)	–	–
Age at first hospitalization. Mean (SD) age +	–	34.73 (10.57)+	–	–
Number of previous hospitalizations. Mean (SD)	–	1.57 (1.83)	–	–
Number of past depressive episodes. mean (SD)	–	3.61 (2.29)	–	–
Time since last depressive episode (months)	–		–	–
Mean (SD)	–	32.83 (28.73)	–	–
Range	–	3–115	–	–

calculated according to Sackeim (2001).
+ calculated with N = 15 as 8 patients had not been hospitalized.
* p < .05.
** p < .01.

Material and methods

Participants

Twenty-six remitted patients with MDD and 26 healthy controls (HC), matched for age, sex, handedness, and education participated in the study. Three patients and one control had to be excluded from the analysis due to technical problems at the time of measurement or excessive movement artifacts in the fMRI data, leaving N = 23 remitted patients with major depression and 25 controls for data analyses (see Table 1 for demographic and illness-related characteristics of the final sample).

Patients were recruited at the Central Institute of Mental Health (Mannheim, Germany) and through local psychotherapists, psychiatrists and patient support groups. DSM-IV diagnoses of major depression and potential comorbid mental disorders were assessed with the German version of the Structured Clinical Interview for DSM-IV, SCID-I and -II (First et al., 1997), conducted by trained psychologists. None of the patients currently fulfilled the criteria for any other mental disorder. Remission from a depressive episode was defined as a score below 5 on the Hamilton Depression Rating Scale (Hamilton, 1960) for at least 8 weeks. At the time of the scan, 9 patients were taking antidepressant medication (see Table 1). Medication load was calculated according to Sackeim (2001) and included as a covariate in all analyses.

Healthy participants were recruited through the registry office of the city of Mannheim and advertisement in public facilities. They were free of past or present mental disorder according to DSM-IV.

Exclusion criteria for all participants were any history of neurological disorder, head trauma with loss of consciousness, metal implants or large tattoos with metal containing color, current and lifetime substance abuse or dependence and age below 18 or above 65 years.

All participants gave informed written consent. The study was approved by the local ethics committee (Medical Faculty Mannheim, University of Heidelberg).

Experimental paradigm and procedure

The details of the experimental paradigm (see Fig. 1) have been described elsewhere (Kanske et al., 2011). In short, participants were presented with emotional (16 negative, 16 positive, highly arousing) and neutral (16 low arousing) images (from the International Affective Picture System, IAPS; Lang et al., 2005) and required to simply view the pictures (view condition) or to down-regulate the emotional response by either reappraising the meaning of the stimuli (reappraisal condition) or by distraction from the images by solving an arithmetic task (distraction condition). Each picture was presented once in each condition (except for neutral images, which were not presented in the reappraisal condition) yielding 128 pseudo-randomly presented trials. Instructions regarding the condition were displayed after an initial emotion induction phase (1 s) as a semi-transparent overlay on the images. The regulation phase (6 s) was followed by a rating of participants' current emotional state on a 9-point scale using the Self-Assessment Manikins ranging from unpleasant to pleasant (4 s). Six training trials were presented prior to the experiment, to familiarize participants with the procedure and practice the emotion regulation strategies. Before the experiment started, the experimenter ensured that reappraisal strategies were employed as intended by inquiring participants about the strategies they used. To ensure that patients and controls perceived images similarly emotional, all participants rated each image in arousal and valence after the experiment, again using the 9-point scale and the Self-Assessment Manikins. In addition, participants rated the difficulty and effort required for each condition, to ensure that different results for reappraisal and distraction were not due to differences in task difficulty.

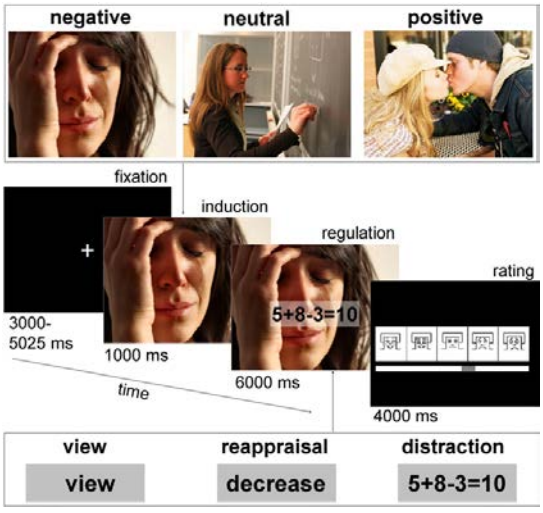


Fig. 1. Sequence of events in a trial. The example pictures resemble those in the experiment, but are not part of the IAPS. Adapted from Kanske et al. (2011), by permission of Oxford University Press.

MRI data acquisition

MRI data were collected on a 3 T scanner (Magnetom TIM Trio, Siemens Medical Solutions, Erlangen, Germany) at the Central Institute of Mental Health, Mannheim. A high-resolution T1-weighted 3D image was acquired (slice thickness = 1.1 mm, FOV = 256 mm × 256 mm × 256 mm, matrix = 256 × 256 × 256). Functional images were obtained from 40 gradient-echo T2*-weighted slices (slice thickness = 2.3 mm) per volume. A single shot echo planar sequence with parallel imaging GRAPPA-technique (acceleration factor 2) was used with a TR of 2700 ms, a flip angle of 90°, TE = 27 ms, FOV = 220 × 220 mm^2, matrix = 96 × 96, and a slice gap of 0.7 mm.

fMRI data analysis

Image processing and statistical analysis was done with SPM8 (http://www.fil.ion.ucl.ac.uk/). Functional images were realigned, slice-time corrected, and spatially normalized using the Montreal Neurological Institute (MNI) template. For normalization images were resampled every 3 mm using sinc interpolation. Images were smoothed using a 9 × 9 × 9 mm Gaussian kernel.

Individual participants' data were analyzed using a General Linear Model for blood oxygen level dependent (BOLD) signal changes due to the experimental conditions. Movement parameters calculated during realignment were included as parameters of no interest. Individual statistical parametric maps were calculated to elucidate: (1) the emotional response per se (view negative vs. view neutral and view positive vs. view neutral), (2) the distraction effect (distraction negative vs. view negative and distraction positive vs. view positive), and (3) the reappraisal effect (reappraisal negative vs. view negative and reappraisal positive vs. view positive).

Two types of second-level random-effects analyses were conducted: (1) One-sample t-tests were calculated on the above mentioned individual contrast images for patients and controls separately. (2) To evaluate differences between patients and controls, two-sample t-tests were computed for all the contrasts.

For all analyses, anatomically defined regions of interests (ROI) from the automated anatomical labeling atlas in WFU PickAtlas v2.0

(Tzourio-Mazoyer et al., 2002) were used to examine activations in the amygdala and the regulation networks as defined in our previous investigation of reappraisal and distraction (Kanske et al., 2011). These included middle and inferior OFC, dlPFC (middle frontal gyrus), dmPFC (superior medial cortex), ACC, and parietal cortices (inferior and superior parietal cortex). Activations were thresholded at FWE-corrected $p<.05$. Medication load was included as a covariate of no interest in all analyses including patients.

Statistical analyses of behavioral data

The emotional state ratings during the experiment were analyzed with PASW (Version 18.0.1, SPSS Inc., Chicago, IL). A one-way ANOVA was conducted to analyze the effect of the emotional picture presentation (negative, neutral, positive) on emotional state in the viewing condition. A $2\times3\times2$ repeated-measures ANOVA including the factors emotion (negative, positive), task (distraction, view, reappraisal), and group (MDD, HC) was calculated to elucidate the effects of regulation on emotional state. The neutral condition was neglected for the second analysis as there were no neutral pictures in the reappraisal condition. The arousal and valence ratings of the pictures after the experiment were analyzed with one-way repeated measures ANOVAs. All effects with a $p<.05$ were treated as statistically significant.

Results

Behavioral data

Post-experimental valence and arousal rating

The rating of the images after the regulation experiment yielded the same pattern as the normative IAPS ratings (see supplemental data ST1). Negative and positive pictures were rated as more arousing than neutral pictures ($F(1,46)=90.2$, $p<.001$; $F(1,46)=125.0$, $p<.001$, respectively). Valence was also significantly different between the picture sets (positive > neutral > negative; $F(1,46)=293.3$, $p<.001$; $F(1,46)=113.9$, $p<.001$, respectively). There were no differences between MDD patients and HCs (all $p>.45$).

Online valence rating

Analysis of the emotional state ratings after each trial (see Fig. 2) revealed a significant main effect of emotion in the viewing condition ($F(2,90)=125.8$, $p<0.001$). Planned comparisons showed that negative and positive trials differed from neutral trials indicating successful emotion induction (negative vs. neutral: $F(1,45=227.7$, $p<0.001$; positive vs. neutral: $F(1,45)=94.9$, $p<0.001$). There were no differences between MDD patients and HCs (all $p>.46$).

The second analysis regarding the regulation effects showed significant main effects of emotion ($F(1,90)=238.8$, $p<0.001$) and task ($F(1,90)=7.4$, $p<.01$), and an interaction of emotion and task ($F(2,180)=56.4$, $p<0.001$). Repeated contrasts regarding the interaction indicated that emotional pictures were rated less negative or positive during distraction and reappraisal compared with the view condition (all $p<.001$). There were no differences between MDD patients and HCs (all $p>.40$).

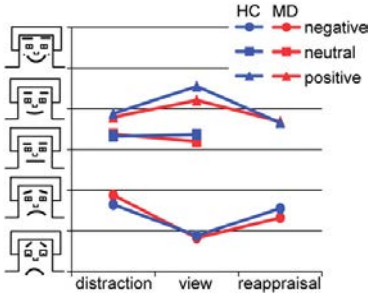


Fig. 2. Emotional state ratings during the experiment. The means of SAM-valence-rating are displayed.

Effort rating

The ratings of effort and difficulty of the two regulation tasks yielded no significant differences between conditions and no differences between MDD patients and HCs (all $p>.45$)

fMRI data

Within-group analyses

Within-group analyses largely replicated our previous findings in both groups (see Kanske et al., 2011), for a complete list of activations see supplemental data ST2). Emotional stimuli elicited increased amygdala activity in comparison to neutral images, which was reduced when participants regulated emotion through either reappraisal or distraction. This reduction was not significant for negative emotional stimuli in MDD patients. The regulation conditions recruited fronto-parietal control networks including dlPFC, and parietal cortex, as well as dmPFC and anterior cingulate for distraction and OFC for reappraisal.

Between-group analyses

Group comparisons yielded no differences for the contrast of viewing emotional vs. neutral images. However, we found increased left amygdala activation for negative emotional stimuli in the reappraisal contrast when comparing MDD patients to HCs (see Fig. 3), indicating that patients were less successful in down-regulating amygdala activity to negative pictures using reappraisal. We did not find this pattern for positive emotional stimuli or for the distraction condition. We also observed altered activity in the regulatory networks. Activation in the right OFC was increased in MDD

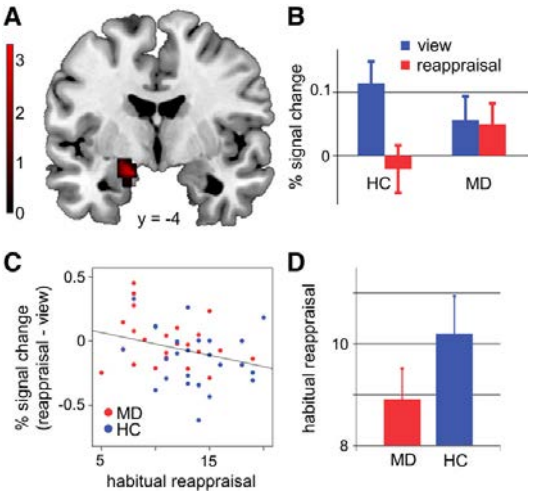


Fig. 3. (A) Increased activation in the left amygdala ($x=-15$, $y=-1$, $z=-14$, $Cs=18$, $T=3.07$, $Z=2.91$) for MDD patients compared to healthy controls in the reappraisal vs. view contrast for negative images and (B) the respective % signal change. (C) The difference in % signal change between the reappraisal and view conditions correlated negatively with habitual reappraisal use in the CERQ ($r=-.30$, $p<.05$), which (D) was also decreased in MDD patients ($t(46)=2.6$, $p<.05$). For graphical display MRIcroN (http://www.cabiatl.com/mricro/mricron/index.html) was used with the MNI template brain.

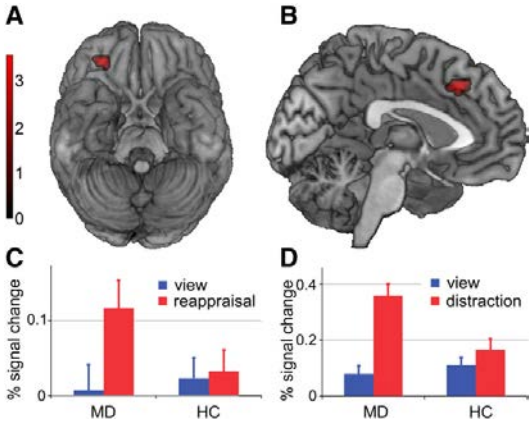


Fig. 4. Increased activation in the regulatory control networks in MDD patients compared to healthy controls during (A, C) reappraisal in the right OFC (x = 30, y = 44, z = −11, Cs = 35, T = 3.91, Z = 3.6) and (B, D) distraction in the left dmPFC (x = −6, y = 26, z = 40, Cs = 167, T = 3.9, Z = 3.6). For graphical display MRIcroN (http://www.cabiatl.com/mricro/mricron/index.html) was used with the MNI template brain.

patients during reappraisal of negative emotional stimuli and increased activation in the dmPFC/ACC during distraction from negative stimuli (see Fig. 4).

Correlational analyses

Comparing MDD patients and controls in the Cognitive Emotion Regulation Questionnaire (CERQ; Garnefski and Kraaij, 2007) subscales yielded a number of significant differences including the habitual use of positive reappraisal (for a complete list of the scales see Table 2). As hypothesized, patients reported less reappraisal use than HCs (see Fig. 3). To test the relation of habitual reappraisal use to the observed impairment in amygdala regulation in MDD patients, we correlated individual scores of all participants in positive reappraisal to the down-regulation in BOLD activity in the amygdala due to reappraisal. Here we found a negative correlation, indicating that participants high in habitual reappraisal show a stronger down-regulation of amygdala activity to negative images using reappraisal. A logistic regression confirmed that the correlation was independent of participants group ($p > .80$). There were no significant correlations with activity in the control networks. As an approximation to measuring competencies in distraction, we used the Adult Temperament Questionnaire (ATQ; Rothbart et al., 2000), including the scale attentional control, measuring the capacity to focus attention as well as to shift attention when desired. Here, MDD patients scored significantly below HCs (see Table 2), but there were no correlations with brain activity ($p > .20$).

We found no significant correlations with any of the measures of current symptoms including BDI, HAMD, and ADS (all $p > .10$). In the patient group only, we also tested for correlations with clinical characteristics. There were no correlations with the number of previous episodes, time since the last episode, number of hospitalizations or age at first hospitalization, and age at the onset of the disease (all $p > .20$).

Table 2
Means and standard deviations (in parentheses) of the CERQ and ATQ subscales in each group are displayed. Significant differences are marked with an asterisk.

		HC	MD	p-Value
CERQ	Self-blame	8.1 (1.4)	9.7 (2.6)	<.05*
	Blaming others	6.1 (2.0)	7.6 (2.9)	<.05*
	Rumination	8.2 (2.3)	10.8 (3.2)	<.05*
	Catastrophizing	5.6 (1.3)	8.0 (2.7)	<.05*
	Putting into perspective	13.6 (4.0)	11.6 (4.1)	<.10
	Positive refocusing	10.2 (3.7)	8.9 (2.9)	>.10
	Positive reappraisal	13.6 (3.4)	11.0 (3.5)	<.05*
	Acceptance	11.0 (3.9)	11.8 (2.7)	>.10
	Refocus on planning	12.6 (3.3)	11.5 (2.7)	> .10
ATQ	Effortful control	5.1 (0.8)	4.6 (0.8)	<.05*
	Inhibitory control	5.3 (0.7)	4.8 (0.8)	<.10
	Activation control	5.0 (1.0)	4.7 (0.8)	>.10
	Attentional control	5.1 (0.9)	4.4 (1.0)	<.05*

* $p < .05$.

Discussion

The present results yield new insights into the crucial role of emotion regulation deficits in depression. We extend previous findings of impaired down-regulation of amygdala activity in currently symptomatic MDD patients to the remitted state. We also show that this amygdala effect is specific to reappraisal and not general to all emotion regulation strategies. Interestingly, to achieve amygdala down-regulation, patients show compensatory hyperactivation in the respective regulatory network for both emotion regulation strategies tested here, reappraisal and distraction. Furthermore, we find that these alterations are selectively present for negative, but not positive emotions, and are related to differences in habitual reappraisal use in depression. The observed impairment of amygdala regulation in depression did not translate to the subjective emotional state ratings. Patients reported similar decreases in current emotion as healthy controls. This underscores the importance of sensitive measures like fMRI to detect changes in emotion regulation mechanisms that are not overtly observable during remission.

A number of questionnaire studies have described emotion regulation impairments as crucial factors in the development and maintenance of depression (Aldao et al., 2010; Garnefski and Kraaij, 2007; Gross and John, 2003). Habitual reappraisal use seems to be negatively related to depressive symptoms, while rumination, catastrophizing, or suppression are increased in depressed patients (Garnefski and Kraaij, 2007; Gross and John, 2003). Our questionnaire data replicate this pattern and further demonstrate, that low habitual use of positive reappraisal, as present in MDD patients, is also related to less successful down-regulation of amygdala activity when using reappraisal in the experimental setting. This result bridges the gap between emotion regulation in everyday life and in neuroimaging experiments. It is in line with data from a simple emotional viewing paradigm that also observed a negative relation of amygdala activity and habitual reappraisal (Drabant et al., 2009).

It is interesting that patients do not show increased levels of amygdala activity during viewing of emotionally negative stimuli, as some studies reported this effect (Siegle et al., 2007; Surguladze et al., 2005). Others, however, did not find elevated amygdala responding to emotional stimuli (Beauregard et al., 1998; Frodl et al., 2009), including the two studies on emotion regulation in depression that also presented a neutral reference condition (Beauregard et al., 2006; Erk et al., 2010). Lee et al. (2007) also found no direct increase of amygdala activity, but a correlation with symptom severity, which might explain the discrepancy. A critical difference between these and the present study is that they investigated patients with a current episode of major depression, while only remitted patients were included here. A study by Sheline et al. (2001) could show that the elevated amygdala responding during an episode is normalized after treatment, which is in line with the lack of a difference in amygdala activity in the viewing condition in the present study and suggests that it is a state-, not a trait-marker of depression.

The finding of deficient regulation of amygdala activity in remitted MDD patients with no or only mild subclinical symptoms extends the previous data on impairments in currently depressed patients

(Beauregard et al., 2006; Erk et al., 2010; Johnstone et al., 2007). It suggests that the difficulties in regulating negative emotions are one of the critical factors that make remission such a vulnerable state with relatively high relapse rates (Hardeveld et al., 2010). It is an interesting question that remains to be tested, if the deficits are directly predictive of subsequent recurrence measures. The independence of emotion regulation impairments from current MDD symptomatology, symptom severity, and clinical characteristics identifies them as trait- rather than state-markers of the disorder. As such, it might also be a useful vulnerability marker of major depression that allows earlier detection of MDD diagnosis; however, this has to be tested in unaffected high-risk individuals (e.g., first-degree relatives of MDD patients).

The present data also show that different emotion regulation strategies are differentially affected in depression. As suggested by previous results on emotion regulation in symptomatic MDD patients, reappraisal is impaired, which is evident in reduced amygdala down-regulation (Beauregard et al., 2006) and altered activity in the regulatory network (Erk et al., 2010; Johnstone et al., 2007). We only found deficient amygdala down-regulation when patients used reappraisal to regulate emotions but not when using a distraction strategy. Interestingly, in healthy participants, distraction has been shown to yield a stronger and more extended down-regulation of the amygdala response to emotional stimuli (Kanske et al., 2011; McRae et al., 2010), which also seems to hold true for remitted MDD patients. However, activation in the control network was enhanced during both strategies. Here we found hyperactivation in the dmPFC for distraction and the OFC for reappraisal, brain regions that were previously identified to be selectively engaged in the respective emotion regulation strategies (Kanske et al., 2011). In line with a number of studies on cognitive control, this enhanced control-related activation can be interpreted as a decrease in neural efficiency (e.g. Gray et al., 2005). Neural inefficiency is typically characterized by enhanced task-related neural activation, either in the absence of any behavioral effects, or associated with poorer performance (Callicott et al., 2000; Wagner et al., 2006). The activation increase is thought to be (partially) compensatory, thus preventing (further) behavioral deficits. In addition to the behavioral data, in emotion regulation studies the activity of the amygdala also serves as a measure of regulation success (Kalisch, 2009). Therefore, the results for the two regulation strategies tested here suggest that depressed participants require additional neural resources to perform the regulation tasks. For distraction, a complete compensation is possible as amygdala activity and emotional state ratings do not differ between patients and controls. For reappraisal, in contrast, no amygdala down-regulation was observed. Unlike the dmPFC hyperactivation during distraction, the OFC activation increase, thus, seems not to compensate amygdala control under negative emotional stimulation. As in our previous study, this suggests that the regulatory effects of distraction are more robust than during reappraisal (Kanske et al., 2011). The psychological differences between the strategies could give an explanation for this differentiation as distraction involves shifting attention away from the emotional content of the stimuli, while reappraisal requires focusing on these aspects in order to reinterpret their meaning. This potentially leads to stronger activation in the ventral emotional stream for the reappraisal as compared with the distraction condition, making it more difficult to reduce the activity. Furthermore, even though the two strategies are not perceived as differently difficult, there are more possible reinterpretation options that could be generated during reappraisal, than solutions for the arithmetic problems that need to be generated during distraction, i.e. the reappraisal task is by definition less strongly specified and also less directive, which might be a particular challenge for MDD patients. In addition, the respective neural networks underlying the two strategies might suffer different degrees of structural changes in depression, which have been more consistently reported for the OFC than the dmPFC (for a meta-analysis see Arnone et al., 2012). Even though MDD patients are able to down-regulate amygdala activity during distraction, the increased dmPFC activity shows that this strategy can also not be applied normally. This result corresponds to studies showing impaired cognitive inhibition in tasks like the Stroop or Wisconsin Card Sorting Test (Gohier et al., 2009), which have been shown to also correlate with temperamental effortful and attentional control as measured in the present study (Rueda et al., 2005). In a recent model, Joormann (2010) suggested that this cognitive deficit might underlie impaired emotion regulation through unsuccessful prevention of negative emotion entering and remaining in working memory.

Despite the similarities of the present data and previous results on emotion regulation through reappraisal in symptomatic MDD patients, there are also a number of differences. Only one of the three currently published studies found deficient down-regulation of amygdala activity that we observed in remitted patients (Beauregard et al., 2006). Johnstone et al. (2007) reported altered connectivity of amygdala and vmPFC during reappraisal, but no direct amygdala activity difference between patients and controls. This is most probably due to differences in the applied experimental design, as the authors also failed to find reduced amygdala activity during reappraisal in healthy controls and in other samples (Urry et al., 2006). In contrast, Erk et al. (2010) reported amygdala down-regulation in healthy participants, but – as Johnstone et al. – did not observe alterations in MDD patients. They found, however, lasting amygdala down-regulation in controls when confronted with the emotional material again, while patients showed no lasting regulation effects. A possible reason for the discrepancy to the present study might lie in the different treatment of medication. Erk et al. (2010) included medicated patients, but did not control for medication in the analyses, whereas we included medication load as a covariate in all analyses. It may, therefore, be that medication normalizes amygdala activity during reappraisal, a question that should be directly tested in future studies including large enough subsamples of unmedicated and medicated patients.

The present data also show a selective deficit in regulating negative emotions. Regarding positive emotion, neither amygdala activity, nor activation in the regulatory networks was altered during reappraisal or distraction when comparing MDD patients to controls. This adds to our understanding of emotion regulation in depression as all previous studies only reported data from negative emotional stimuli (Beauregard et al., 2006; Erk et al., 2010; Johnstone et al., 2007). It is a plausible result given that depression is a disorder dominated by negative affect and related symptoms of low self-esteem and loss of interest and pleasure in activities. In contrast to the unaffected down-regulation of positive emotion, there is evidence that MDD patients have problems in enhancing or sustaining positive affect using cognitive emotion regulation (Heller et al., 2009). In future studies it would be interesting to directly contrast the up- and down-regulation of emotion in depressed patients, which might yield reverse patterns for positive and negative affect.

Regarding the clinical relevance of the present results, they underline the importance of addressing emotion regulation deficits in psychotherapeutic interventions. As the deficits are not only present in currently depressed patients, but persist when patients recover, they are a continuing vulnerability factor and suitable treatment may have the potential to reduce relapse rates. Because of the documented advantageous effects of reappraisal, for instance on well-being (Gross and John, 2003), and the observed deficit in reappraisal in particular, this strategy should be a focus of treatment. Nevertheless, as patients are well able to use distraction to regulate emotions, and as distraction has been shown to have strong effect on amygdala activity (Kanske et al., 2011; McRae et al., 2010), this strategy could proof useful to manage states of immediate intense negative emotion. Using reappraisal enhances the memory for regulated stimuli, which is an indicator of its potential for long-term effects (Dillon et al., 2007). Future studies should specify the long-term emotion

regulatory effects of both strategies to further guide psychotherapeutic interventions.

There are some limitations to the present study. As described above, the remitted patients kept receiving optimal antidepressant medication (9 of 23) to prevent withdrawal or emergence of depressive symptoms. However, this does not allow testing the "pure" disease effects. We tried to control for this by including a composite medication load measure as a covariate in all analyses (Sackeim, 2001). Future studies should aim at assembling larger sample sizes that allow direct contrasts of medicated and unmedicated patients or even of subgroups with different medication. Larger sample sizes would also be desirable to validate the correlational results of questionnaire measures and brain activation. A further point is the specificity of the observed emotion regulation deficits to depression. A number of questionnaire studies showed altered emotion regulation across different diagnoses (Berking et al., 2008) and there is also some indication that these deficits can be observed on the neural level in different diagnoses (Modinos et al., 2010; Schulze et al., 2011). It is a possibility that impaired emotion regulation is a truly transdiagnostic issue. However, previous studies mainly applied reappraisal as regulation strategy and often only include negative emotional stimuli. Therefore, it might also be possible to differentiate patient groups when testing different emotion regulation strategies, responses to emotional stimuli of different valence separately, and complex patterns of hypo- and hyperactivations in limbic and in control regions.

To conclude, our findings suggest that individuals with major depression suffer from a deficit in down-regulating negative emotions that extends into remission. These results are consistent with the hypothesis that impaired emotion regulation is a trait-marker for depression, which underscores the importance of addressing emotion regulation as specific treatment target. The data also show the need for future studies that assess the success of therapeutic interventions on a neural basis and specify underlying treatment mechanisms.

Acknowledgment

We wish to thank Johanna Forneck and Heike Schmidt for help with the data acquisition and two anonymous reviewers for their helpful comments on a previous version of this manuscript.

The present work was funded by a grant from the Deutsche Forschungsgemeinschaft (We3638/3-1).

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.neuroimage.2012.03.089.

References

Aldao, A., Nolen-Hoeksema, S., Schweizer, S., 2010. Emotion-regulation strategies across psychopathology: a meta-analytic review. Clin. Psychol. Rev. 30, 217–237.
Arnone, D., McIntosh, A.M., Ebmeier, K.P., Munafo, M.R., Anderson, I.M., 2012. Magnetic resonance imaging studies in unipolar depression: systematic review and meta-regression analyses. Eur. Neuropsychopharmacol. 22, 1–16.
Beauregard, M., Leroux, J.M., Bergman, S., Arzoumanian, Y., Beaudoin, G., Bourgouin, P., Stip, E., 1998. The functional neuroanatomy of major depression: an fMRI study using an emotional activation paradigm. Neuroreport 9, 3253–3258.
Beauregard, M., Paquette, V., Levesque, J., 2006. Dysfunction in the neural circuitry of emotional self-regulation in major depressive disorder. Neuroreport 17, 843–846.
Berking, M., Wupperman, P., Reichardt, A., Pejic, T., Dippel, A., Znoj, H., 2008. Emotion-regulation skills as a treatment target in psychotherapy. Behav. Res. Ther. 46, 1230–1237.
Callicott, J.H., Bertolino, A., Mattay, V.S., Langheim, F.J., Duyn, J., Coppola, R., Goldberg, T.E., Weinberger, D.R., 2000. Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. Cereb. Cortex 10, 1078–1092.
Dannlowski, U., Ohrmann, P., Konrad, C., Domschke, K., Bauer, J., Kugel, H., Hohoff, C., Schoning, S., Kersting, A., Baune, B.T., Mortensen, L.S., Arolt, V., Zwitserlood, P., Deckert, J., Heindel, W., Suslow, T., 2009. Reduced amygdala–prefrontal coupling in major depression: association with MAOA genotype and illness severity. Int. J. Neuropsychopharmacol. 12, 11–22.
Dillon, D.G., Ritchey, M., Johnson, B.D., LaBar, K.S., 2007. Dissociable effects of conscious emotion regulation strategies on explicit and implicit memory. Emotion 7, 354–365.
Disner, S.G., Beevers, C.G., Haigh, E.A., Beck, A.T., 2011. Neural mechanisms of the cognitive model of depression. Nat. Rev. Neurosci. 12, 467–477.
Drabant, E.M., McRae, K., Manuck, S.B., Hariri, A.R., Gross, J.J., 2009. Individual differences in typical reappraisal use predict amygdala and prefrontal responses. Biol. Psychiatry 65, 367–373.
Drevets, W.C., 2007. Orbitofrontal cortex function and structure in depression. Ann. N. Y. Acad. Sci. 1121, 499–527.
Drevets, W.C., Price, J.L., Bardgett, M.E., Reich, T., Todd, R.D., Raichle, M.E., 2002. Glucose metabolism in the amygdala in depression: relationship to diagnostic subtype and plasma cortisol levels. Pharmacol. Biochem. Behav. 71, 431–447.
Erk, S., Mikschl, A., Stier, S., Ciaramidaro, A., Gapp, V., Weber, B., Walter, H., 2010. Acute and sustained effects of cognitive emotion regulation in major depression. J. Neurosci. 30, 15726–15734.
First, M.B., Gibbon, M., Spitzer, R.L., Williams, J.B.W., 1997. Structured Clinical Interview for DSM IV Axis I Disorders (SCID-I). American Psychiatric Publishing, Inc., Arlington.
Frodl, T., Scheuerecker, J., Albrecht, J., Kleemann, A.M., Muller-Schunk, S., Koutsouleris, N., Moller, H.J., Bruckmann, H., Wiesmann, M., Meisenzahl, E., 2009. Neuronal correlates of emotional processing in patients with major depression. World J. Biol. Psychiatry 10, 202–208.
Garnefski, N., Kraaij, V., 2007. The Cognitive Emotion Regulation Questionnaire: psychometric features and prospective relationships with depression and anxiety in adults. Eur. J. Psychol. Assess. 23, 141–149.
Gohier, B., Ferracci, L., Surguladze, S.A., Lawrence, E., El Hage, W., Kefi, M.Z., Allain, P., Garre, J.B., Le Gall, D., 2009. Cognitive inhibition and working memory in unipolar depression. J. Affect. Disord. 116, 100–105.
Gray, J.R., Burgess, G.C., Schaefer, A., Yarkoni, T., Larsen, R.J., Braver, T.S., 2005. Affective personality differences in neural processing efficiency confirmed using fMRI. Cogn. Affect. Behav. Neurosci. 5, 182–190.
Gross, J.J., 2001. Emotion regulation in adulthood: timing is everything. Curr. Dir. Psychol. Sci. 10, 214–219.
Gross, J.J., John, O.P., 2003. Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. J. Pers. Soc. Psychol. 85, 348–362.
Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.
Hardeveld, F., Spijker, J., De Graaf, R., Nolen, W.A., Beekman, A.T., 2010. Prevalence and predictors of recurrence of major depressive disorder in the adult population. Acta Psychiatr. Scand. 122, 184–191.
Heller, A.S., Johnstone, T., Shackman, A.J., Light, S.N., Peterson, M.J., Kolden, G.G., Kalin, N.H., Davidson, R.J., 2009. Reduced capacity to sustain positive emotion in major depression reflects diminished maintenance of fronto-striatal brain activation. Proc. Natl. Acad. Sci. U. S. A. 106, 22445–22450.
Johnstone, T., van Reekum, C.M., Urry, H.L., Kalin, N.H., Davidson, R.J., 2007. Failure to regulate: counterproductive recruitment of top-down prefrontal–subcortical circuitry in major depression. J. Neurosci. 27, 8877–8884.
Joormann, J., 2010. Cognitive inhibition and emotion regulation in depression. Curr. Dir. Psychol. Sci. 19, 161–166.
Joormann, J., Gotlib, I.H., 2010. Emotion regulation in depression: relation to cognitive inhibition. Cogn. Emot. 24, 281–298.
Kalisch, R., 2009. The functional neuroanatomy of reappraisal: time matters. Neurosci. Biobehav. Rev. 33, 1215–1226.
Kanske, P., Heissler, J., Schonfelder, S., Bongers, A., Wessa, M., 2011. How to regulate emotion? Neural networks for reappraisal and distraction. Cereb. Cortex 21, 1379–1388.
Lang, P.J., Bradley, M.M., Cuthbert, B.N., 2005. International affective picture system (IAPS): affective ratings of pictures and instruction manual. Technical Report A-6. Center for Research in Psychophysiology, University of Florida, Gainesville, Florida.
Lee, B.T., Seong Whi, C., Hyung Soo, K., Lee, B.C., Choi, I.G., Lyoo, I.K., Ham, B.J., 2007. The neural substrates of affective processing toward positive and negative affective pictures in patients with major depressive disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry 31, 1487–1492.
Liotti, M., Mayberg, H.S., McGinnis, S., Brannan, S.L., Jerabek, P., 2002. Unmasking disease-specific cerebral blood flow abnormalities: mood challenge in patients with remitted unipolar depression. Am. J. Psychiatry 159, 1830–1840.
McRae, K., Hughes, B., Chopra, S., Gabrieli, J.D., Gross, J.J., Ochsner, K.N., 2010. The neural bases of distraction and reappraisal. J. Cogn. Neurosci. 22, 248–262.
Modinos, G., Ormel, J., Aleman, A., 2010. Altered activation and functional connectivity of neural systems supporting cognitive control of emotion in psychosis proneness. Schizophr. Res. 118, 88–97.
Ochsner, K.N., Gross, J.J., 2005. The cognitive control of emotion. Trends Cogn. Sci. 9, 242–249.
Ritchey, M., Dolcos, F., Eddington, K.M., Strauman, T.J., Cabeza, R., 2011. Neural correlates of emotional processing in depression: changes with cognitive behavioral therapy and predictors of treatment response. J. Psychiatr. Res. 45, 577–587.
Rothbart, M.K., Ahadi, S.A., Evans, D.E., 2000. Temperament and personality: origins and outcomes. J. Pers. Soc. Psychol. 78, 122–135.
Rueda, M.R., Rothbart, M.K., McCandliss, B.D., Saccomanno, L., Posner, M.I., 2005. Training, maturation, and genetic influences on the development of executive attention. Proc. Natl. Acad. Sci. U. S. A. 102, 14931–14936.
Sackeim, H.A., 2001. The definition and meaning of treatment-resistant depression. J. Clin. Psychiatry 62 (Suppl. 16), 10–17.

Schulze, L., Domes, G., Kruger, A., Berger, C., Fleischer, M., Prehn, K., Schmahl, C., Grossmann, A., Hauenstein, K., Herpertz, S.C., 2011. Neuronal correlates of cognitive reappraisal in borderline patients with affective instability. Biol. Psychiatry 69, 564–573.

Segal, Z.V., Gemar, M., Williams, S., 1999. Differential cognitive response to a mood challenge following successful cognitive therapy or pharmacotherapy for unipolar depression. J. Abnorm. Psychol. 108, 3–10.

Sheline, Y.I., Barch, D.M., Donnelly, J.M., Ollinger, J.M., Snyder, A.Z., Mintun, M.A., 2001. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. Biol. Psychiatry 50, 651–658.

Siegle, G.J., Thompson, W., Carter, C.S., Steinhauer, S.R., Thase, M.E., 2007. Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. Biol. Psychiatry 61, 198–209.

Surguladze, S., Brammer, M.J., Keedwell, P., Giampietro, V., Young, A.W., Travis, M.J., Williams, S.C., Phillips, M.L., 2005. A differential pattern of neural response toward sad versus happy facial expressions in major depressive disorder. Biol. Psychiatry 57, 201–209.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage 15, 273–289.

Urry, H.L., van Reekum, C.M., Johnstone, T., Kalin, N.H., Thurow, M.E., Schaefer, H.S., Jackson, C.A., Frye, C.J., Greischar, L.L., Alexander, A.L., Davidson, R.J., 2006. Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. J. Neurosci. 26, 4415–4425.

Wagner, G., Sinsel, E., Sobanski, T., Kohler, S., Marinou, V., Mentzel, H.J., Sauer, H., Schlosser, R.G., 2006. Cortical inefficiency in patients with unipolar depression: an event-related FMRI study with the Stroop task. Biol. Psychiatry 59, 958–965.

Supplemental data ST1

Mean valence and arousal ratings and standard deviations (in parentheses) for the picture selection. Normative IAPS ratings and the ratings of the present samples are displayed.

	normative IAPS ratings		*MD ratings*		*HC ratings*	
	valence	arousal	valence	arousal	valence	arousal
negative	1.87 (0.21)	6.28 (0.64)	2.47 (1.17)	6.05 (1.51)	2.55 (0.81)	5.99 (1.54)
neutral	4.92 (0.28)	2.98 (0.34)	5.22 (0.50)	2.10 (1.43)	5.25 (0.37)	2.53 (1.55)
positive	7.38 (0.39)	6.29 (0.68)	6.73 (1.06)	4.41 (1.81)	6.66 (0.82)	4.83 (1.33)

Supplemental data ST2

Within-groups analyses for Healthy controls and MD patients.

	H	MNI coordinates			Cs	T	Z
		x	y	z			
Healthy controls							
view positive - view neutral							
amygdala	L	-21	-1	-11	25	3.58	3.17
	R	24	2	-11	42	3.19	2.88
view negative - view neutral							
amygdala	L	-24	-4	-14	59	4.95	4.07
	R	21	-1	-11	69	4.34	3.69
temporal/occipital	L	-30	-79	-14	224	9.09	5.93
	R	12	-85	4	537	10.7	6.42
thalamus	R	3	-7	1	24	7.7	5.41
view positive - reappraisal positive							
amygdala	L	-21	-7	-17	46	3.45	3.08
	R	30	-4	-20	75	3.58	3.17
view negative - reappraisal negative							
amygdala	L	-24	-7	-17	69	4.49	3.78
	R	27	-4	-20	66	3.08	2.8
occipital	R	24	-61	46	13	7.75	5.43
view positive - distraction positive							
amygdala	L	-24	-4	-17	77	7.62	5.38
	R	30	-4	-20	87	7.68	5.41
middle temporal	L	-60	-4	-23	77	9.88	6.19
	R	54	-67	7	401	12.3	6.85
fusiform gyrus	R	39	-43	-20	72	11.4	6.63
middle occipital	L	-51	-76	13	152	8.98	5.89
superior occipital	L	-12	-97	28	62	7.08	5.16
	R	15	-95	25	96	6.85	5.05
ventromedial frontal	L/R	0	35	-8	670	8.63	5.77
view negative - distraction negative							
amygdala	L	-21	-4	-23	77	4.73	3.94
	R	33	-1	-26	79	4.8	3.98
middle temporal	L	-54	-73	16	58	8.04	5.55
	R	51	-67	-2	345	9.44	6.05
superior occipital	L	-6	-94	28	76	8.44	5.7
	R	15	-97	19	140	8.25	5.62
fusiform gyrus	R	42	-43	-23	58	7.23	5.22
ventromedial frontal	L/R	0	38	-20	175	10.1	6.26
reappraisal positive - view positive							
inferior parietal/angular	L	-57	-52	37	162	4.52	3.8
	R	60	-55	40	181	4.15	3.57
middle frontal #	L	-45	20	49	110	3.81	3.34
middle orbitofrontal	L	-42	47	-5	34	3.31	2.97
reappraisal negative - view negative							
inferior parietal/angular	L	-48	-67	40	172	4.82	3.99
	R	51	-64	43	74	3.68	3.25
distraction positive - view positive							
inferior/superior parietal/angular	L	-24	-70	46	1046	7.91	5.5
	R	33	-67	46	749	6.09	4.69

superior frontal	L	-27	-1	64	182	5.78	4.53
	R	24	8	61	152	4.88	4.03
middle frontal	L	-48	29	31	195	6.33	4.81
	R	36	38	19	389	4.29	3.66
anterior cingulate/superior medial frontal	L	3	26	49	79	4.46	3.77
	R	9	29	28	111	5.04	4.12
insula	L	-30	20	1	129	4.8	3.98
	R	36	20	-5	129	5.48	4.37
distraction negative - view negative							
inferior/superior parietal/angular	L	-27	-58	46	1142	7.44	5.31
	R	36	-46	40	813	5.93	4.61
superior frontal	L	-24	-1	46	177	6.64	4.95
	R	24	53	-2	29	4.5	3.79
middle frontal	L	-24	2	46	138	6.25	4.77
	L	-45	32	28	242	6.1	4.7
	R	39	35	25	721	6.32	4.8
anterior cingulate/superior medial frontal	L	-9	17	40	51	5.48	4.37
	R	9	23	43	83	6.21	4.75
insula	L	-36	14	13	16	3.99	3.46
	R	36	17	7	82	5.94	4.62
MDD patients							
view positive - view neutral							
amygdala #	L	-18	-1	-11	14	2.74	2.51
middle occipital	L	-51	-73	1	102	9.52	5.86
view negative - view neutral							
amygdala	R	33	-4	-20	16	3.23	2.87
superior occipital	L	-18	-61	52	19	7.3	5.1
	R	21	-58	49	97	8.88	5.66
fusiform gyrus	R	27	-61	-5	81	8.23	5.44
lingual gyrus	R	9	-70	-5	74	7.74	5.27
inferior temporal	L	-48	-73	-2	34	6.82	4.9
	R	48	-70	-5	59	7.21	5.06
view positive - reappraisal positive							
amygdala	L	-18	-7	-17	35	3.75	3.24
view negative - reappraisal negative							
-							
view positive - distraction positive							
amygdala	L	-21	-7	-17	62	4.19	3.53
	R	21	-4	-17	49	3.32	2.94
middle temporal	R	54	-70	7	98	8.79	5.64
inferior temporal	L	-42	2	-38	22	7.53	5.19
superior occipital	L	-9	-100	16	65	9.17	5.76
	R	12	-94	22	191	9.18	5.76
view negative - distraction negative							
amygdala	L	-27	-4	-20	63	6.2	4.62
	R	30	-4	-20	69	5.91	4.49
middle temporal	R	51	-70	4	112	10.7	6.2
superior occipital	L	-9	-97	19	15	7.29	5.09
	R	24	-88	40	129	7.77	5.28
reappraisal positive - view positive							
inferior parietal/angular	L	-45	-61	43	260	4.12	3.48
inferior/middle orbitofrontal	L	-36	44	-8	48	3.92	3.36
reappraisal negative - view negative							

inferior orbitofrontal	L	-39	41	-14	23	4.51	3.73
inferior/middle orbitofrontal	R	36	47	-11	38	3.83	3.3
distraction positive - view positive							
inferior/superior parietal/angular	L	-45	-43	52	832	12.8	6.69
	R	45	-43	49	465	12.8	6.68
middle frontal	L	-45	38	22	203	11.4	6.36
	L	-30	2	58	82	7.37	5.13
	R	39	41	19	282	11.6	6.42
	R	30	8	55	85	8.38	5.5
anterior cingulate/superior medial frontal	R	15	26	25	239	7.82	5.29
insula	L	-39	11	1	420	8.3	5.47
distraction negative - view negative							
inferior/superior parietal/angular	L	-36	-46	40	1508	17.7	7.56
	R	39	-46	43		12	6.51
middle frontal	L	-45	35	25	751	9.63	5.81
	R	30	11	55	87	10.4	6.11
	R	36	38	28	154	11.6	6.43
anterior cingulate/superior medial frontal	L/R	9	14	46	401	9.97	5.99
insula	R	33	20	4	65	8.16	5.42

H. hemisphere; CS. cluster size in number of activated voxels; L. left; R. right; T- and Z-values for each peak are given. # $p < .10$

Supplemental data ST3

Means and standard deviations (in parentheses) of the CERQ and ATQ subscales in each group are displayed. Significant differences are marked with an asterisk.

		HC	MD	p
CERQ	Self-blame	8.1 (1.4)	9.7 (2.6)	< .05*
	Blaming Others	6.1 (2.0)	7.6 (2.9)	< .05*
	Rumination	8.2 (2.3)	10.8 (3.2)	< .05*
	Catastrophizing	5.6 (1.3)	8.0 (2.7)	< .05*
	Putting into Perspective	13.6 (4.0)	11.6 (4.1)	< .10
	Positive Refocusing	10.2 (3.7)	8.9 (2.9)	> .10
	Positive Reappraisal	13.6 (3.4)	11.0 (3.5)	< .05*
	Acceptance	11.0 (3.9)	11.8 (2.7)	> .10
	Refocus on Planning	12.6 (3.3)	11.5 (2.7)	> .10
ATQ	Effortful Control	5.1 (0.8)	4.6 (0.8)	< .05*
	Inhibitory Control	5.3 (0.7)	4.8 (0.8)	< .10
	Activation Control	5.0 (1.0)	4.7 (0.8)	> .10
	Attentional Control	5.1 (0.9)	4.4 (1.0)	< .05*

* $p < .05$

Impaired regulation of emotion: Neural correlates of reappraisal and distraction in bipolar disorder and unaffected relatives

Philipp Kanske, PhD[1], Sandra Schönfelder[2], Johanna Forneck[3], Michèle Wessa, PhD[2]

[1]Department of Social Neuroscience, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

[2]Department of Clinical Psychology and Neuropsychology, Johannes Gutenberg University, Mainz, Germany

[3]Section for Experimental Psychopathology and Neuroimaging, Department of General Psychiatry, Center for Psychosocial Medicine, Heidelberg University, Heidelberg, Germany

Running title: Emotion regulation in bipolar disorder

Place where the work was carried out: Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

Corresponding author: Michèle Wessa, Department of Clinical Psychology and Neuropsychology, Johannes Gutenberg University, Wallstr. 3, 55122 Mainz, Germany

phone: +49-6131-39-39259; fax: +49-6131-39-39102; e-mail: wessa@uni-mainz.de

Abstract

Deficient emotion regulation has been proposed as a crucial pathological mechanism in bipolar disorder (BD). We therefore investigated emotion regulation impairments in BD, the related neural underpinnings and their etiological relevance for the disorder. Twenty-two euthymic patients with bipolar-I disorder and 17 unaffected first-degree relatives of BD-I patients, as well as two groups of healthy gender-, age-, and education-matched controls (N = 22/17, respectively) were included. Participants underwent functional magnetic resonance imaging (fMRI) while applying two different emotion regulation techniques, reappraisal and distraction, when presented with emotional images. BD patients and relatives showed impaired down-regulation of amygdala activity during reappraisal, but not during distraction, when compared to controls. This deficit was correlated with the habitual use of reappraisal. The negative connectivity of amygdala and orbitofrontal cortex observed during reappraisal in controls was reversed in BD patients and relatives. There were no significant differences between BD patients and relatives. As being observed in BD patients and unaffected relatives, deficits in emotion regulation through reappraisal may represent heritable neurobiological abnormalities underlying BD. The neural mechanisms include impaired control of amygdala reactivity to emotional stimuli and dysfunctional connectivity of the amygdala to regulatory control regions in the orbitofrontal cortex. These are, thus, important aspects of the neurobiological basis of increased vulnerability for bipolar disorder.

Keywords: mania, depression, affect, amygdala, orbitofrontal cortex, fMRI

Introduction

Bipolar disorder (BD) is a highly heritable, chronic disease characterized by increased affect lability and intensity,[1] elevated emotional reactivity and presumably impaired emotion regulation.[2-4] Even though impairments in the implicit regulation of emotion have been repeatedly observed,[5-8] there are only few reports on the voluntary regulation of emotion[9] in BD.[10, 11] The etiological relevance of deficits in emotion regulation has been suggested by many authors, however empirically it is still unclear, if these deficits emerge during the course of the disease or precede its development, potentially representing increased vulnerability. Furthermore, the neural correlates underlying potential impairments are largely unknown. They are particularly interesting, as neural changes may precede behavioral manifestations in healthy high-risk populations.[12-17]

The regulation of emotion entails implicit, automatic and more voluntary processes that may occur in parallel, but can also be separated experimentally.[2] Both seem to be supported by the interactions of neural circuits underlying emotion generation, including the amygdala, with cognitive control networks, mainly in prefrontal and anterior cingulate cortex.[18-20] Voluntary emotion regulation, in particular, has been suggested to comprise a number of techniques that can be organized along a continuum ranging from attentional control (e.g. the disengagement of attention from emotional stimuli through a distracting task) to cognitive change (e.g. the top-down reappraisal of a certain stimulus).[9] Direct comparisons of reappraisal and distraction in healthy individuals showed common effects in dorsolateral and –medial prefrontal cortex and in the down-regulation of amygdala activity, but also specifics including lateral orbitofrontal involvement in reappraisal, which was related to amygdala down-regulation.[21, 22]

Models of emotion processing in BD[2, 4] propose abnormalities in both, those regions involved in early emotion reactivity and those involved more in the top-down regulation of emotion. A recent meta-analyses on functional magnetic resonance imaging (fMRI) studies in BD corroborates this with the finding of increased parahippocampal gyrus/amygdala activity in response to emotional stimuli.[23] In contrast, BD patients show reduced activation and reduced gray matter in dorsolateral and ventrolateral prefrontal cortex.[23] Consequently, hypo-activation of these structures might lead to a deficit in voluntary down-regulation of exaggerated emotional responses in bipolar patients. On a self-report level, BD patients and unaffected relatives show more frequent use of maladaptive emotion regulation strategies, such as rumination and self-blame, but less frequent use of adaptive strategies, such as putting into perspective.[24, 25] Moreover, previous neuroimaging studies of emotion reactivity and regulation reported altered connectivity between prefrontal and limbic structures, which might underlie the proposed deficit to cognitively regulate emotions in bipolar patients.[5, 10, 11, 26, 27] Thus, the existing self-report and neuroimaging data strongly suggest emotion regulation deficits in bipolar patients. However, so far no study experimentally compared different emotion regulation capacities and their neural underpinnings in bipolar patients and high-risk populations.

Investigations with healthy relatives of BD patients have shown alterations not only in self-reported emotion regulation skills,[25] but also in neural responses to emotional stimuli[28] as well as to cognitive challenges.[29, 30] These studies have, therefore, given rise to the hypothesis, that altered ventral prefrontal-limbic activity and connectivity, critical for the cognitive regulation of emotion, may be a precursor of the disorder.[31, 32] Similarly, alterations in euthymic BD patients have been interpreted as representing a vulnerability trait marker, although healthy individuals at risk to develop

bipolar disorder have not been included in this particular study.[33] The evidence, therefore, suggests impairments in voluntary emotion regulation in BD, which may already manifest in high-risk populations such as unaffected relatives of BD patients. Directly testing this question is both timely and important to identify vulnerability markers that enable early diagnosis and potentially preventive interventions, to refine etiological models, and to develop more specific and targeted psychotherapy for BD.

The present study investigated two cognitive emotion regulation strategies (i.e. reappraisal and distraction) in euthymic patients with BD-I, unaffected first-degree relatives of BD-I patients and respectively matched healthy controls. We used an established experimental paradigm that activates ventral-limbic brain areas related to emotional responses and a prefrontal-parietal network related to emotion regulation in healthy participants.[21] Habitual use of maladaptive and adaptive regulation strategies was assessed with the Cognitive-Emotion-Regulation-Questionnaire (CERQ[34]).

We hypothesized exaggerated emotional responses in BD patients and relatives in self-reports and limbic activity. Similarly, emotion regulation deficits are expected, reflected in reduced down-regulation of the amygdala in emotion regulation conditions. Based on known functional disturbances in dorsolateral and ventrolateral prefrontal as well as parietal cortices in BD patients reduced activation in these brain areas and thus deficient emotion regulation should be observable for distraction as well as reappraisal. Furthermore, we expect that reduced amygdala down-regulation in BD patients and high-risk individuals is mediated by disturbed functional connectivity between prefrontal cortex and limbic brain regions.

Materials and Methods

Participants and Diagnostic Assessment

All participants underwent the Structured Clinical Interview for DSM-IV (SCID-I/-II[35-38]) and screening for exclusion criteria (neurological disorders, head trauma with loss of consciousness, metal implants, tattoos, substance abuse or dependence, age <18 or >65 years). Interviews and observer rating scales for mania (Young Mania Rating Scale; YMRS[39]) and depression (Hamilton Depression Rating Scale; HAMD[40]) were conducted by senior clinical psychologists. Participants completed the Beck Depression Inventory (BDI[41, 42]) and the CERQ[34]. The study was approved by the ethics committee of the Medical Faculty Mannheim, Heidelberg University. All participants provided written informed consent before entering the study.

Sample 1: BD patients and healthy controls

Twenty-two euthymic patients with BD-I and 22 gender-, age- and education-matched healthy volunteers with no history of psychiatric disorders participated (Table 1). Patients were recruited at the Central Institute of Mental Health, Mannheim and through local psychiatrists, psychotherapists, and patient support groups. None of the patients currently met the criteria for any DSM-IV disorder other than BD. A life chart assessing variables related to illness course was completed for all patients. Euthymia was defined as a HAMD score <5 and a YMRS score <7[43]. We inquired about current medication and verified its stability during the past six months. To analyze the psychotropic medication effect, we calculated total medication load according to a published algorithm[44] reflecting both dose and variety of different medication[45]. The composite measure was generated by summing all individual medication codes for each medication category (2.32 [2.08]). We then checked for correlations of this index with the effects of interest in bipolar patients.

Sample 2: Relatives and healthy controls

Seventeen healthy first-degree relatives of BD-I patients and 17 gender-, age- and education-matched healthy controls participated (Table 1). None fulfilled criteria for any mental disorder or took any psychotropic medication. The relatives were not related to those BD patients tested in this study. Five relatives were siblings, 4 were children, and 8 were parents of BD patients. Twelve relatives had one case in the family and 5 relatives had 2 or more cases in the family.

Experimental paradigm and procedure

The experimental paradigm (Figure 1A)[21] confronted participants with 32 emotional, highly arousing (16 negative, 16 positive) and 16 neutral, low arousing images (from the International Affective Picture System, IAPS[46]). They were required to simply view the pictures (view condition) or to down-regulate the emotional response by reinterpreting the meaning of the stimuli (reappraisal condition) or by distraction through an arithmetic task (distraction condition). Each picture was presented once in each condition (except for neutral images, which were not presented in the reappraisal condition) yielding 128 pseudo-randomly presented trials. Instructions regarding the condition were displayed after an initial emotion induction phase (1s) as a semi-transparent overlay on the images. The regulation phase (6s) was followed by a rating of participants' current emotional state on a 9-point scale using the Self-Assessment Manikins ranging from unpleasant to pleasant (4s). Participants were instructed and trained outside the scanner in the application of the emotion regulation strategies. Six additional training trials were presented inside the scanner. In case of any difficulties with the procedure, the practice block was repeated, which resolved all problems as reported by the participants. Participants completed a questionnaire after the

experiment that asked for the applied regulation techniques to ensure correct application of the instructions.

To validate the normative IAPS ratings of the pictures all participants rated each image after the experiment in arousal and valence, again using Self-Assessment Manikins. These ratings were largely compatible with the normative data (Supplement S1).

MRI Data acquisition

MRI data were collected on a 3T Siemens Magnetom TIM Trio at the Central Institute of Mental Health, Mannheim. A high-resolution T1-weighted 3D image was acquired (slice thickness=1.1mm, FOV=256x240x176mm, matrix=256x240x160). Functional images were obtained from 40 gradient-echo T2*-weighted slices (slice thickness=2.3 mm). A single shot echo planar sequence with parallel imaging GRAPPA-technique (acceleration factor 2) was used with TR=2700 ms, flip angle=90°, TE=27ms, FOV=220mm^2, matrix=96x96, slice gap=0.7mm.

fMRI data analysis

Image processing and statistical analyses were done with SPM8 (http://www.fil.ion.ucl.ac.uk/). Functional images were realigned, slice-time corrected, and spatially normalized using the Montreal Neurological Institute (MNI) template. For normalization images were resampled every 3mm using sinc interpolation. Images were smoothed using a 9x9x9mm Gaussian kernel.

Individual participants' data were analyzed using a General Linear Model for blood oxygen level dependent (BOLD) signal changes. Movement parameters calculated during realignment were included as parameters of no interest. Individual statistical

parametric maps were calculated to elucidate: (1) the emotional response per se (view emotional vs. view neutral), (2) the distraction effect (distraction emotional vs. view emotional), and (3) the reappraisal effect (reappraisal emotional vs. view emotional).

Two types of second-level random-effects analyses were conducted: One-sample t-tests were calculated on the above mentioned individual contrast images across patients, unaffected relatives and controls. To evaluate differences between patients and matched controls, relatives and matched controls, and patients and relatives, two-sample t-tests were computed for all the contrasts. For the analyses we averaged across negative and positive stimuli as direct contrasts of these conditions yielded no differences in the emotion regulation networks and to enhance statistical power.[21] As there were no gender differences, we also averaged across male and female participants.

To assess functional connectivity of the amygdala during emotion regulation, we calculated a standard psychophysiological interaction analysis (PPI) as implemented in SPM8.[47] To this end, we extracted the deconvolved time-series from a 5-mm spherical seed region around the peak activation (reappraisal vs. view) in the anatomically defined amygdala ROI as first regressor. The second regressor represented the experimental condition (regulation vs. view), and the regressor of interest was the interaction of the two. A second-level random effects analysis with two-sample t-tests was calculated to compare connectivity differences between the groups.

For all analyses, anatomically defined regions of interests (ROI) from the WFU PickAtlas v2.0[48] were used to examine activations in the amygdala and the regulation networks as observed in our previous investigations of reappraisal and distraction.[21, 49] These included as separate, bilateral masks orbitofrontal (OFC), dorsolateral (dlPFC; middle frontal) and dorsomedial prefrontal (dmPFC, superior medial), anterior

cingulate (ACC), and parietal cortex (inferior, superior). Activations were thresholded at an FWE-corrected $p<0.05$. Additionally, we applied the Bonferroni-Holm method which adjusts the p values that were already corrected for family-wise error rates within each ROI according to the total number of ROIs used in the analyses[50, 51] or accordingly for the number of seed regions in the PPI analysis.[52] Results that were significant at a whole-brain FWE corrected $p<0.05$ level are also reported.

To allow for correlations of the observed activations with the questionnaire and clinical measures, we extracted individual % signal change from the significant cluster in a 5 mm radius sphere around the respective activation peak (if they fell into the respective anatomical ROI, e.g. the amygdala).

Statistical analyses of behavioral data

Emotion ratings were analyzed with SPSS 20.0. First, to analyze the emotional responses to the pictures in the viewing condition, repeated measures ANOVAs with emotion as within-subject factor and group as between-subject factor were calculated. Second, to detect the effects of regulation strategies on emotional state we conducted repeated-measures ANOVAs with emotion and condition as within-subject factors and group as between-subject factor. As there were no neutral pictures in the reappraisal condition, the neutral condition was neglected for the second analysis. For the CERQ data we used t-tests to compare the groups.

Results

Behavioral data

Online emotional state ratings

Analysis of the emotional state ratings (Figure 1B) after each trial yielded a significant main effect of emotion in the viewing condition (Sample 1: $F(2,84)=191.5$, $p<0.001$, Sample 2: $F(2,64)=129.9$, $p<0.001$). Planned comparisons revealed that negative and positive trials differed from each other and from neutral trials indicating successful emotion induction (all $p<0.001$). There were no group effects regarding BD patients and controls (all $p>0.45$), but regarding relatives and their controls there was a significant interaction of emotion and group ($F(2,64)=3.3$, $p<0.05$) indicating less positive ratings of positive stimuli in relatives ($F(1,32)=7.8$, $p<0.01$). Comparing BD patients to relatives showed the same pattern ($F(2,74)=6.4$, $p<0.01$; $F(1,37)=5.8$, $p<0.05$).

Regarding the effects of the different regulation strategies on emotional state, we found a significant main effect of emotion (Sample 1: $F(1,42)=134.3$, $p<0.001$, Sample 2: $F(1,32)=130.3$, $p<0.001$), a main effect of task (Sample 1: $F(2,84)=5.8$, $p<0.01$, Sample 2: $F(2.64)=10.8$, $p<0.001$), as well as a significant interaction of emotion and task (Sample 1: $F(2,84)=48.1$, $p<0.001$, Sample 2: $F(2,64)=43.0$, $p<0.001$). Repeated contrasts regarding the interaction revealed that emotional pictures were rated less negative or positive during distraction and reappraisal as compared to the view condition (all $p<0.001$). There were no group effects regarding BD patients and controls (all $p>0.15$), but regarding relatives and their controls there was a significant interaction of emotion and task with group ($F(2,64)=4.8$, $p<0.05$) indicating stronger down-regulation of positive emotion during reappraisal in controls ($F(1,32)=8.0$, $p<0.01$). There were no differences between BD patients and relatives.

Habitual emotion regulation strategies (CERQ)

We observed significant group differences in maladaptive and adaptive emotion regulation strategies (Supplement S2). BD patients reported more frequent use of rumination, self-blame, and catastrophizing, but less frequent use of positive reappraisal. Relatives also reported less frequent use of positive reappraisal, but there were no differences in the other regulation strategies, including putting into perspective. Comparing BD patients and relatives showed higher scores for patients in rumination, self-blame, and catastrophizing, but no differences in positive reappraisal.

fMRI data

Common effects for emotional responding, reappraisal, and distraction

To assess whether the response to the emotional pictures per se and the two emotion regulation strategies activated the same networks identified previously,[21, 49] we first averaged across all participants. This analysis yielded activation patterns that were largely compatible with our previous data and other reports in the literature (Supplement S3). Amygdala activation (together with ventral temporal and occipital cortex and poster cingulate gyrus/precuneus) was increased in response to emotional stimuli during the view condition. In turn, amygdala activation was reduced in both emotion regulation conditions. The control network for reappraisal included bilateral OFC, dmPFC, dlPFC, and inferior parietal cortices. Distraction also activated dlPFC, dmPFC extending into ACC, insula, and superior parietal cortices.

Group differences

<u>Sample 1: BD patients vs. controls</u>

When comparing activation in BD patients and controls we found no differences in responses to emotional compared to neutral stimuli in the view condition. However, for reappraisal, we observed less down-regulation of left amygdala activity and right amygdala/parahippocampal activity in BD patients (Figure 2, Table 2). There were no differences between the groups in the distraction condition or in activation of the regulatory control networks.

To elucidate changes in amygdala connectivity during reappraisal we conducted a PPI between-group analysis directly contrasting connectivity in the reappraisal vs. view condition in bipolar patients versus healthy controls. Here we found significant differences in connectivity between left amygdala (seed region) and right OFC (Figure 3, Table 2) and ACC, and right amygdala with right OFC. Connectivity during reappraisal between amygdala and OFC and ACC activity was reversed in BD patients compared to healthy controls. While controls showed negative connectivity during reappraisal (i.e. an activation increase in the OFC was associated with activation decrease in the amygdala) BD patients showed positive connectivity between these regions.

Sample 2: Relatives vs. controls

The results in unaffected relatives were largely comparable to those in BD patients. We found no differences in responses to emotional compared to neutral stimuli in the view and distraction conditions, but during reappraisal, relatives showed less down-regulation of amygdala activity than controls (Figure 2, Table 2). There were no differences between the groups in the distraction condition or in activation of the regulatory control networks.

The PPI analysis in sample 2 showed that the connectivity of left amygdala with bilateral OFC (Figure 3) and of right amygdala with right OFC was reversed in relatives

compared to controls. As in sample 1, controls showed negative connectivity during reappraisal, while relatives showed positive connectivity between these regions.

BD patients vs. relatives

There were no differences in activation or connectivity of the amygdala between BD patients and unaffected relatives.

Correlation analysis

When correlating individual reappraisal use with amygdala activity in the reappraisal vs. view condition, we found a significant negative correlation (Figure 2; r=-.37; $p<0.01$), indicating that participants high in habitual reappraisal use are more successful in down-regulating amygdala activity in the experimental setting. This pattern was consistent when calculating correlations in the two samples separately (Sample 1: r=-.35;<.05, Sample 2: r=-.47; $p<0.01$).

We found no significant correlations of amygdala activity with any of the measures of current symptoms including BDI, HAMD, and YMRS (all $p>0.10$). In the patient group only, we also tested for correlations with clinical characteristics. There were no correlations with number of previous episodes, time since last episode, number of hospitalizations or age at first hospitalization, age at onset of the disease, or medication load (all $p>0.20$).

Discussion

We investigated cognitive emotion regulation and its neural correlates in BD-I patients and unaffected relatives, which revealed several important results. First, BD patients showed an emotion regulation deficit with respect to amygdala down-regulation during the reappraisal condition, mediated by reduced altered connectivity between OFC and amygdala. Interestingly, this regulation deficit was only present in the reappraisal condition, not during distraction. Second, these results were also observed in unaffected relatives, with increased genetic risk to develop BD in the future, which suggests their interpretation as a vulnerability marker for BD. As the relatives are not affected by previous disorder episodes, the deficit does not seem to be a consequence of but a predisposition for the development of the illness. As the relatives are unmedicated, the observed impairments are not an artifact of medication in BD patients. Third, the deficient down-regulation of amygdala activity is paralleled by the self-report of impaired habitual reappraisal, which gives an indication of the ecological validity of the experimental effect.

The pattern of limbic hyperactivation and altered connectivity with frontal regions is in line with the suggestion of impaired prefrontal control over emotion generating regions like the amygdala in BD.[2] However, it further characterizes the conditions of this impairment. We observed altered amygdala activity in patients and relatives only in the reappraisal condition, not during simple viewing of emotional stimuli. This contrasts other reports of increased amygdala responses to mildly sad faces[8] and facial affect matching.[7] However, there are also reports of lacking amygdala group differences, or even blunted amygdala responding to emotional stimuli in depressed BD patients.[53, 54] Such inconsistencies have been found during euthymia as well.[55, 56] As these studies did not explicitly instruct participants how to treat arising

emotions it is possible that patients and controls applied regulation differently, potentially in line with their habitual use of emotion regulation.[25] By explicitly instructing the use of certain regulation strategies, the present study allowed studying the specific effects of strategies, which could offer an explanation for the discrepant previous results.

The present data also differentiate between regulation strategies. The observed deficit was only present in the reappraisal, not the distraction condition. This is in line with recent evidence in unipolar depression, where amygdala regulation was also selectively impaired during reappraisal.[49] Together with data from healthy participants, where the effect of distraction on amygdala activity is stronger and more extended,[21, 22] this suggests that the regulatory effects of distraction are more robust and less prone to impairment than reappraisal. A possible reason could be that while distraction shifts attention away from the emotional content of a stimulus, reappraisal requires focusing on these aspects in order to reinterpret their meaning. Furthermore, even though difficulty of the conditions did not differ between the groups (Supplement S4), the reappraisal task is by definition less specified and directive than the distraction condition as there are more reappraisal options than solutions for the arithmetic problems. This seems to be a particular challenge for BD patients and relatives.

The reappraisal deficit in BD patients and relatives was also present in the self-report of habitual emotion regulation use (CERQ). In addition, dysfunctional regulation strategies such as rumination, catastrophizing and self-blame were reported more frequently in BD patients (but not unaffected relatives), which is in line with a recent study using the same questionnaire.[25] This study did, however, not find a decrease in reappraisal use as reported here. It is possible that this lack of a reappraisal difference is due to age differences between patients and controls in that study, as age has been

shown to influence emotion regulation and also reappraisal specifically.[57] It is intriguing that the habitual use of reappraisal correlates with the amygdala down-regulation effect during experimental reappraisal, which also corroborates the ecological validity of our experimental procedure.

Surprisingly and in contrast to the neural activation patterns, subjective affect ratings during the experiment were not affected in BD. In contrast, relatives of BD patients showed a smaller reduction in positive affect during reappraisal than controls. This effect is most likely due to the reduced potential of the positive stimuli to induce emotion in this group, as shown in relatives' lower valence ratings for positive stimuli during the viewing condition. Interestingly, an opposite effect was observed for post-hoc ratings of the images after the experiment, where relatives rated pictures more positively. This suggests some volatility in positive affect in the relatives, who may be more sensitive to external factors like the scanner environment, while currently euthymic BD patients have a more stable subjective evaluation of their current affect, potentially due to previous treatments. A dissociation between preserved behavioral performance and altered neural activation during cognitive-emotional tasks has been observed before in euthymic BD patients.[13] Euthymia might thus indeed be a recovered state where measures like fMRI are more sensitive than behavioral ones to pick up altered emotional processing.

There are limitations to the present study. Patients with differing medical status were tested. The lack of a significant correlation with medication load[44], suggests that medication does not play an important role for the effects, which is further supported by the results in the unmedicated healthy relatives. It has to be interpreted with great care nevertheless as the load score was originally designed for the evaluation of treatment adequacy and resistance. However, the use of this type of composite

measures of total psychotropic medication load has been recommended for neuroimaging studies in bipolar disorder[45] and this particular score has been used previously[50, 58]. Larger sample sizes could allow delineating the exact effects of different medications in future studies. Including symptomatic patients in future studies would have the additional potential to elucidate if emotion regulation varies with the symptomatic status of bipolar patients in the sense of mood-congruent valence effects. We focused on a priori defined regions of interest based on previous investigations regarding the neural networks involved in emotion regulation,[21, 49] future studies with larger sample sizes should also test for whole-brain differences between the tested groups. While the presence of alterations in healthy individuals at increased risk to develop a disorder has consistently been interpreted as indication vulnerability,[59-61] future longitudinal studies could allow much stronger conclusions regarding the etiological relevance of the observed deficits (cf. [62]).

To conclude, we found an emotion regulation deficit in euthymic BD patients and unaffected relatives when applying a reappraisal, but not a distraction strategy, indicated by impaired down-regulation of amygdala activity and altered connectivity with OFC. That healthy individuals at increased genetic risk of developing bipolar disorder do show the deficit indicates that it may represent a vulnerability marker. The presence of the impairment during remission also highlights it as a crucial treatment target, which should also be assessed with sensitive neuroimaging methods.

Acknowledgments

This research was funded by a grant from the Deutsche Forschungsgemeinschaft (We3638/3-1).

We wish to thank Heike Schmidt and Janine Heissler for their help with the data acquisition. We also thank six anonymous reviewers for their helpful comments on a previous version of the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Henry C, Van den Bulke D, Bellivier F, Roy I, Swendsen J, M'Bailara K*, et al*. Affective lability and affect intensity as core dimensions of bipolar disorders during euthymic period. *Psychiatry Res* 2008; **159:** 1-6.

2. Phillips ML, Ladouceur CD, Drevets WC. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. *Molecular psychiatry* 2008; **13:** 829, 833-857.

3. Wessa M, Kanske P, Linke J. Bipolar disorder: a neural network perspective on a disorder of emotion and motivation. *Restorative neurology and neuroscience* 2014; **32:** 51-62.

4. Wessa M, Linke J. Emotional processing in bipolar disorder: behavioural and neuroimaging findings. *Int Rev Psychiatry* 2009; **21:** 357-367.

5. Almeida JR, Versace A, Mechelli A, Hassel S, Quevedo K, Kupfer DJ*, et al*. Abnormal amygdala-prefrontal effective connectivity to happy faces differentiates bipolar from major depression. *Biol Psychiatry* 2009; **66:** 451-459.

6. Strakowski SM, Eliassen JC, Lamy M, Cerullo MA, Allendorfer JB, Madore M*, et al*. Functional magnetic resonance imaging brain activation in bipolar mania: evidence for disruption of the ventrolateral prefrontal-amygdala emotional pathway. *Biol Psychiatry* 2011; **69:** 381-388.

7. Altshuler L, Bookheimer S, Proenza MA, Townsend J, Sabb F, Firestine A*, et al*. Increased amygdala activation during mania: a functional magnetic resonance imaging study. *Am J Psychiatry* 2005; **162:** 1211-1213.

8. Almeida JR, Versace A, Hassel S, Kupfer DJ, Phillips ML. Elevated amygdala activity to sad facial expressions: a state marker of bipolar but not unipolar depression. *Biol Psychiatry* 2010; **67:** 414-421.

9. Ochsner KN, Gross JJ. The cognitive control of emotion. *Trends Cogn Sci* 2005; **9:** 242-249.

10. Morris RW, Sparks A, Mitchell PB, Weickert CS, Green MJ. Lack of cortico-limbic coupling in bipolar disorder and schizophrenia during emotion regulation. *Translational psychiatry* 2012; **2:** e90.

11. Townsend JD, Torrisi SJ, Lieberman MD, Sugar CA, Bookheimer SY, Altshuler LL. Frontal-amygdala connectivity alterations during emotion downregulation in bipolar I disorder. *Biol Psychiatry* 2013; **73:** 127-135.

12. Elliott R, Ogilvie A, Rubinsztein JS, Calderon G, Dolan RJ, Sahakian BJ. Abnormal ventral frontal response during performance of an affective go/no go task in patients with mania. *Biol Psychiatry* 2004; **55:** 1163-1170.

13. Wessa M, Houenou J, Paillere-Martinot ML, Berthoz S, Artiges E, Leboyer M*, et al*. Fronto-striatal overactivation in euthymic bipolar patients during an emotional go/nogo task. *Am J Psychiatry* 2007; **164:** 638-646.

14. Heissler J, Kanske P, Schonfelder S, Wessa M. Inefficiency of emotion regulation as vulnerability marker for bipolar disorder: Evidence from healthy individuals with hypomanic personality. *J Affect Disord* 2013.

15. Bertocci MA, Bebko GM, Mullin BC, Langenecker SA, Ladouceur CD, Almeida JR*, et al*. Abnormal anterior cingulate cortical activity during emotional n-back task performance distinguishes bipolar from unipolar depressed females. *Psychological medicine* 2012; **42:** 1417-1428.

16. Deckersbach T, Rauch SL, Buhlmann U, Ostacher MJ, Beucke JC, Nierenberg AA*, et al*. An fMRI investigation of working memory and sadness in females with bipolar disorder: a brief report. *Bipolar Disord* 2008; **10:** 928-942.

17. Kanske P, Heissler J, Schonfelder S, Forneck J, Wessa M. Neural correlates of emotional distractibility in bipolar disorder patients, unaffected relatives, and individuals with hypomanic personality. *Am J Psychiatry* 2013; **170:** 1487-1496.

18. Etkin A, Egner T, Peraza DM, Kandel ER, Hirsch J. Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron* 2006; **51:** 871-882.

19. Gyurak A, Gross JJ, Etkin A. Explicit and implicit emotion regulation: a dual-process framework. *Cogn Emot* 2011; **25:** 400-412.

20. Ochsner KN, Silvers JA, Buhle JT. Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. *Ann N Y Acad Sci* 2012; **1251:** E1-24.

21. Kanske P, Heissler J, Schonfelder S, Bongers A, Wessa M. How to regulate emotion? Neural networks for reappraisal and distraction. *Cereb Cortex* 2011; **21:** 1379-1388.

22. McRae K, Hughes B, Chopra S, Gabrieli JD, Gross JJ, Ochsner KN. The neural bases of distraction and reappraisal. *Journal of cognitive neuroscience* 2010; **22:** 248-262.

23. Houenou J, Frommberger J, Carde S, Glasbrenner M, Diener C, Leboyer M*, et al*. Neuroimaging-based markers of bipolar disorder: evidence from two meta-analyses. *J Affect Disord* 2011; **132:** 344-355.

24. Wolkenstein L, Zwick JC, Hautzinger M, Joormann J. Cognitive emotion regulation in euthymic bipolar disorder. *J Affect Disord* 2014; **160:** 92-97.

25. Green MJ, Lino BJ, Hwang EJ, Sparks A, James C, Mitchell PB. Cognitive regulation of emotion in bipolar I disorder and unaffected biological relatives. *Acta Psychiatr Scand* 2011; **124:** 307-316.

26. Foland LC, Altshuler LL, Bookheimer SY, Eisenberger N, Townsend J, Thompson PM. Evidence for deficient modulation of amygdala response by prefrontal cortex in bipolar mania. *Psychiatry Res* 2008; **162:** 27-37.

27. Wang F, Kalmar JH, He Y, Jackowski M, Chepenik LG, Edmiston EE*, et al*. Functional and structural connectivity between the perigenual anterior cingulate and amygdala in bipolar disorder. *Biol Psychiatry* 2009; **66:** 516-521.

28. Surguladze SA, Marshall N, Schulze K, Hall MH, Walshe M, Bramon E*, et al*. Exaggerated neural response to emotional faces in patients with bipolar disorder and their first-degree relatives. *NeuroImage* 2010; **53:** 58-64.

29. Thermenos HW, Goldstein JM, Milanovic SM, Whitfield-Gabrieli S, Makris N, Laviolette P*, et al*. An fMRI study of working memory in persons with bipolar disorder or at genetic risk for bipolar disorder. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics* 2010; **153B:** 120-131.

30. Whalley HC, Sussmann JE, Chakirova G, Mukerjee P, Peel A, McKirdy J*, et al*. The neural basis of familial risk and temperamental variation in individuals at high risk of bipolar disorder. *Biol Psychiatry* 2011; **70:** 343-349.

31. Strakowski SM, Adler CM, Almeida J, Altshuler LL, Blumberg HP, Chang KD*, et al*. The functional neuroanatomy of bipolar disorder: a consensus model. *Bipolar Disord* 2012; **14:** 313-325.

32. Strakowski SM, Delbello MP, Adler CM. The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. *Molecular psychiatry* 2005; **10:** 105-116.

33. Versace A, Thompson WK, Zhou D, Almeida JR, Hassel S, Klein CR*, et al*. Abnormal left and right amygdala-orbitofrontal cortical functional connectivity to emotional faces: state versus trait vulnerability markers of depression in bipolar disorder. *Biol Psychiatry* 2010; **67:** 422-431.

34. Garnefski N, Kraaij V. The Cognitive Emotion Regulation Questionnaire: Psychometric features and prospective relationships with depression and anxiety in adults. *Eur J Psychol Assess* 2007; **23:** 141-149.

35. First MB, Gibbon M, Spitzer RL, Williams JBW. *Structured Clinical Interview for DSM IV Axis I Disorders (SCID-I).* American Psychiatric Publishing, Inc.: Arlington, 1997.

36. Wittchen H-U, Zaudig M, Fydrich T. *SKID-I. Strukturiertes Klinisches Interview für DSM-IV [Structural Clinical Interview for DSM-IV Axis I Disorders].* Hogrefe: Göttingen, 1997.

37. First MB, Gibbon M, Spitzer RL, Williams JBW, Benjamin L. *Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II).* . American Psychiatric Publishing, Inc.: Arlington, 1997.

38. Wittchen H-U, Zaudig M, Fydrich T. *SKID-II. Strukturiertes Klinisches Interview für DSM-IV [Structural Clinical Interview for DSM-IV Axis II Disorders].* Hogrefe: Göttingen, 1997.

39. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *The British journal of psychiatry : the journal of mental science* 1978; **133:** 429-435.

40. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; **23:** 56-62.

41. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961; **4:** 561-571.

42. Hautzinger M, Keller F, Kühner C. *BDI-II. Beck-Depressions-Inventar. Revision.* Pearson Assessment: Frankfurt, 2009.

43. Mercer L, Becerra R. A unique emotional processing profile of euthymic bipolar disorder? A critical review. *J Affect Disord* 2013; **146:** 295-309.

44. Sackeim HA. The definition and meaning of treatment-resistant depression. *J Clin Psychiatry* 2001; **62 Suppl 16:** 10-17.

45. Phillips ML, Travis MJ, Fagiolini A, Kupfer DJ. Medication effects in neuroimaging studies of bipolar disorder. *Am J Psychiatry* 2008; **165:** 313-320.

46. Lang PJ, Bradley MM, Cuthbert BN (2005). International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical report A-6. Center for Research in Psychophysiology, University of Florida: Gainesville, Florida.

47. Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ. Psychophysiological and modulatory interactions in neuroimaging. *NeuroImage* 1997; **6:** 218-229.

48. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, *et al*. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage* 2002; **15:** 273-289.

49. Kanske P, Heissler J, Schonfelder S, Wessa M. Neural correlates of emotion regulation deficits in remitted depression: The influence of regulation strategy, habitual regulation use, and emotional valence. *NeuroImage* 2012; **61:** 686-963.

50. Linke J, King AV, Rietschel M, Strohmaier J, Hennerici M, Gass A, *et al*. Increased Medial Orbitofrontal and Amygdala Activation: Evidence for a Systems-Level Endophenotype of Bipolar I Disorder. *Am J Psychiatry* 2012.

51. Ogawa K, Inui T. Neural representation of observed actions in the parietal and premotor cortex. *NeuroImage* 2011; **56:** 728-735.

52. Connolly CG, Wu J, Ho TC, Hoeft F, Wolkowitz O, Eisendrath S*, et al*. Resting-state functional connectivity of subgenual anterior cingulate cortex in depressed adolescents. *Biol Psychiatry* 2013; **74:** 898-907.

53. Altshuler L, Bookheimer S, Townsend J, Proenza MA, Sabb F, Mintz J*, et al*. Regional brain changes in bipolar I depression: a functional magnetic resonance imaging study. *Bipolar Disord* 2008; **10:** 708-717.

54. Malhi GS, Lagopoulos J, Ward PB, Kumari V, Mitchell PB, Parker GB*, et al*. Cognitive generation of affect in bipolar depression: an fMRI study. *The European journal of neuroscience* 2004; **19:** 741-754.

55. Foland-Ross LC, Bookheimer SY, Lieberman MD, Sugar CA, Townsend JD, Fischer J*, et al*. Normal amygdala activation but deficient ventrolateral prefrontal activation in adults with bipolar disorder during euthymia. *NeuroImage* 2012; **59:** 738-744.

56. Lagopoulos J, Malhi GS. A functional magnetic resonance imaging study of emotional Stroop in euthymic bipolar disorder. *Neuroreport* 2007; **18:** 1583-1587.

57. Urry HL, Gross JJ. Emotion regulation in older age. *Curr Dir Psychol Sci* 2010; **19:** 352-357.

58. Almeida JR, Akkal D, Hassel S, Travis MJ, Banihashemi L, Kerr N*, et al*. Reduced gray matter volume in ventral prefrontal cortex but not amygdala in bipolar disorder: significant effects of gender and trait anxiety. *Psychiatry Res* 2009; **171:** 54-68.

59. Seidman LJ, Faraone SV, Goldstein JM, Kremen WS, Horton NJ, Makris N*, et al*. Left hippocampal volume as a vulnerability indicator for schizophrenia: a magnetic resonance imaging morphometric study of nonpsychotic first-degree relatives. *Arch Gen Psychiatry* 2002; **59:** 839-849.

60. Frangou S. Risk and resilience in bipolar disorder: rationale and design of the Vulnerability to Bipolar Disorders Study (VIBES). *Biochemical Society transactions* 2009; **37:** 1085-1089.

61. Durston S, Mulder M, Casey BJ, Ziermans T, van Engeland H. Activation in ventral prefrontal cortex is sensitive to genetic vulnerability for attention-deficit hyperactivity disorder. *Biol Psychiatry* 2006; **60:** 1062-1070.

62. Phillips ML, Swartz HA. A critical appraisal of neuroimaging studies of bipolar disorder: toward a new conceptualization of underlying neural circuitry and a road map for future research. *Am J Psychiatry* 2014; **171:** 829-843.

Figure legends

Figure 1: (A) Sequence of events in a trial. The example pictures resemble those in the experiment, but are not part of the IAPS. (B) Emotional state ratings during the experiment. The means of SAM-valence-ratings are displayed for BD patients (left), healthy relatives (right) and their respective controls.

Figure 2: Increased amygdala activation during reappraisal for BD patients (A) and relatives (B) compared to their respective controls as well as % signal change in the left amygdala. The difference in % signal change between the reappraisal and view conditions correlated negatively with habitual reappraisal use in the CERQ (C), which was also decreased in BD patients and relatives (D).

Figure 3: OFC regions of reversed functional connectivity to the left amygdala in BD patients (A) and healthy relatives (B) compared to their respective controls.

Tables

Table 1: Sample characteristics for BD patients + controls and relatives + controls.

	Sample 1				**Sample 2**				**BD compared to Rel**	
	BD N = 22	*Con* N = 22	*Statistics*	*p-value*	*Rel* N = 17	*Con* N = 17	*Statistics*	*p-value*	*Statistics*	*p-value*
Gender ratio (female/male)	14/8	12/10	$Chi^2(1)=.38$	p=0.540	8/9	8/9	$Chi^2(1)=0$	p=1	$Chi^2(1)=1.07$	p=0.301
Age. mean (SD)	39.4 (11.8)	40.5 (11.8)	t(42)=-.29	p=0.770	36.7 (16.3)	35.94 (15.63)	t(32)=.13	p=0.898	t(37)=.31	p=0.759
Years of education. mean (SD)	11.3 (1.6)	11.8 (1.5)	t(42)=-1.06	p=0.293	12.5 (1.2)	12.88 (0.33)	t(32)=-1.39	p=0.175	t(37)=-2.69	p=0.011*
Intelligence score (MWT-B). mean (SD)	105.4 (12.6)	107.7 (14.4)	t(41)=-.54	p=0.592	103.1 (11.8)	109.4 (12.8)	t(30)=-1.45	p=0.157	t(35)=.26	p=0.797
Married lifetime. No. (%)	12 (55.0)	13 (59.1)	$Chi^2(1)=.09$	p=0.761	11 (64.7)	6 (35.3)	$Chi^2(1)=2.94$	p=0.169	$Chi^2(1)=.41$	p=0.522
Currently employed. No. (%)	13 (59.1)	21 (95.5)	$Chi^2(1)=8.28$	p=0.004**	15 (88.2)	15 (88.2)	$Chi^2(1)=0$	p=1	$Chi^2(1)=4.02$	p=0.045*
Handedness: LQ-scores. mean (SD)	83.8 (13.8)	85.7 (23.1)	t(41)=-.34	p=0.736	57.7 (64.8)	80.1 (41.1)	t(30)=-1.20	p=0.238	t(35)=1.68	p=0.071
Current symptoms										
YMRS. mean (SD)	1.0 (1.6)	0 (0)	t(40)=2.96	p=0.008**	0 (0)	0 (0)	-	-	t(36)=2.49	p=0.018*
HAMD. mean (SD)	0.7 (1.2)	.10 (.4)	t(40)=2.31	p=0.029*	0.3 (1.0)	0.13 (0.50)	t(31)=.62	p=0.543	t(36)=1.34	p=0.189
BDI. mean (SD)	6.7 (6.0)	1.2 (2.1)	t(42)=4.05	p<0.001**	3.0 (3.3)	1.76 (3.11)	t(32)=1.08	p=0.289	t(37)=2.61	p=0.013*
BDI. affective subscale. mean (SD)	4.00 (4.5)	.7 (1.3)	t(42)=3.34	p=0.003**	1.4 (1.9)	1.06 (2.41)	t(32)=.40	p=0.694	t(37)=2.60	p=0.013*
BDI. somatic subscale. mean (SD)	2.7 (2.0)	.6 (1.1)	t(42)=4.56	p<0.001**	1.6 (1.8)	0.71 (0.98)	t(32)=1.80	p=0.082	t(37)=2.11	p=0.042*
Course of illness										
Age at onset. mean (SD)	25.2 (7.7)	-	-	-	-	-	-	-	-	-
Age at first hospitalization. mean (SD)	27.3 (8.2)	-	-	-	-	-	-	-	-	-
No. of hospitalization. mean (SD)	3.2 (2.5)	-	-	-	-	-	-	-	-	-
No. of depressive episodes. mean (SD)	3.6 (2.4)	-	-	-	-	-	-	-	-	-
No. of manic episodes. mean (SD)	3.0 (1.8)	-	-	-	-	-	-	-	-	-
Time in remission (months). mean (SD)	54.0 (69.0)	-	-	-	-	-	-	-	-	-
Substances										
Regular caffeine. No. (%)	14 (66.7)	17 (81.0)	$Chi^2(1)=1.11$	p=0.292	10 (62.5)	13 (81.3)	$Chi^2(1)=1.40$	p=0.433	$Chi^2(1)=.07$	p=0.793
Regular nicotine. No. (%)	6 (28.6)	2 (9.1)	$Chi^2(1)=2.69$	p=0.101	2 (12.5)	1 (5.9)	$Chi^2(1)=.44$	p=0.601	$Chi^2(1)=1.38$	p=0.239
Regular alcohol. No. (%)	7 (31.8)	9 (40.9)	$Chi^2(1)=.39$	p=0.531	6 (35.3)	7 (41.2)	$Chi^2(1)=.13$	p=1	$Chi^2(1)=.05$	p=0.819

Medication use											
None No. (%)	3 (13.6)	-	-	-	-	-	-	-	-	-	
Antidepressants. No. (%)	7 (31.8)	-	-	-	-	-	-	-	-	-	
Benzodiazepines. No. (%)	1 (4.5)	-	-	-	-	-	-	-	-	-	
Antipsychotics. No. (%)	12 (54.5)	-	-	-	-	-	-	-	-	-	
Lithium carbonate. No. (%)	8 (36.4)	-	-	-	-	-	-	-	-	-	
Valproic acid. No. (%)	11 (50.0)	-	-	-	-	-	-	-	-	-	
Lamotrigine. No. (%)	6 (27.3)	-	-	-	-	-	-	-	-	-	

* $p < .05$
** $p < .01$

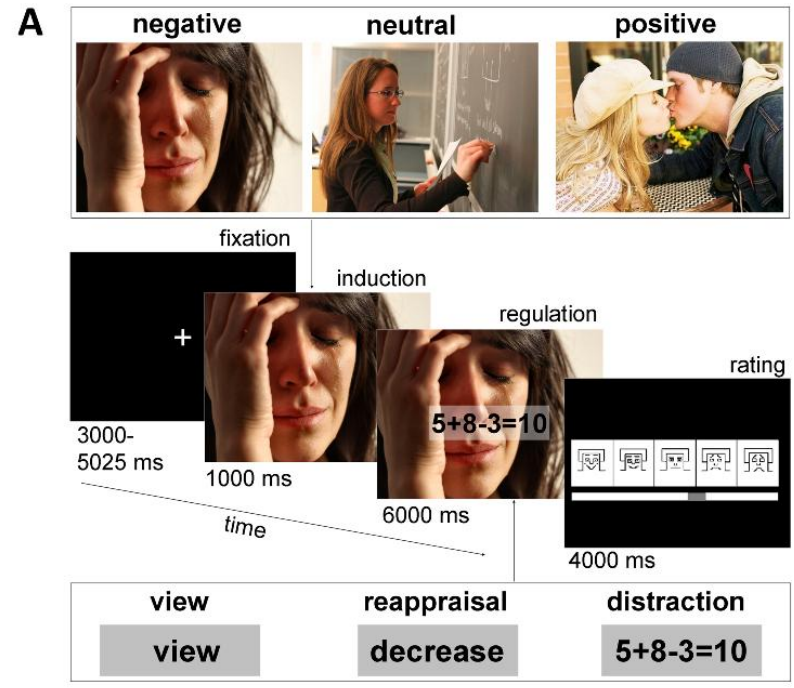
Table 2: Activation differences between BD patients, relatives, and their respective controls; and PPI results.

	H	BA	MNI coordinates			Cs	Z	T
			x	y	z			
Rel>Con: reappraisal - view emotional								
amygdala	L		-21	-7	-14	20	3.06	3.32
	R		33	5	-20	26	2.87	3.09
ventral ACC	L	10	-12	50	-2	108	4.20	4.90
insula	L	48	-39	2	-11	69	3.36	3.71
	R	48	36	-16	1	161	3.84	4.37
BD>Con: reappraisal - view emotional								
amygdala	L		-15	-4	-17	18	2.99	3.18
amygdala / parahippocampal	R		21	5	-26	60	4.31	4.87
BD>Con: PPI L-amygdala seed								
orbitofrontal	L	47	-42	35	-8	53	4.94	5.79
BD>Con: PPI R-amygdala seed								
orbitofrontal	L	47	-12	50	-5	23	4.41	5.01
Rel>Con: PPI L-amygdala seed								
orbitofrontal	L	47	-39	29	-14	60	4.45	5.29
	R	47	36	56	-8	15	4.59	5.52
Rel>Con: PPI R-amygdala seed								
orbitofrontal	R	47	39	56	-5	49	5.06	6.33

H = Hemisphere; BA = Brodmann area of the peak activation; CS = Cluster size in number of activated voxels

Figures

Figure 1



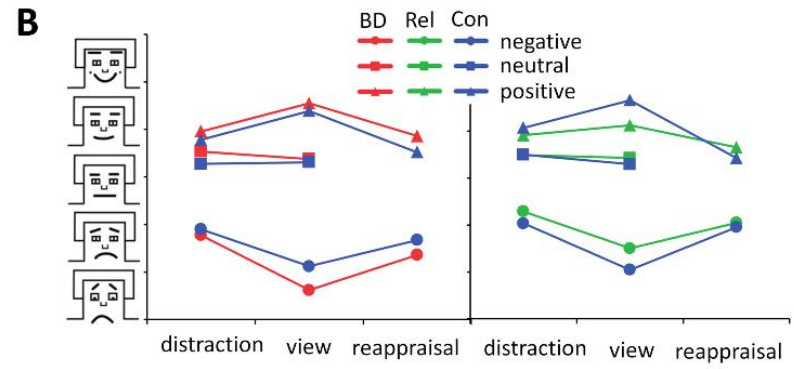


Figure 2

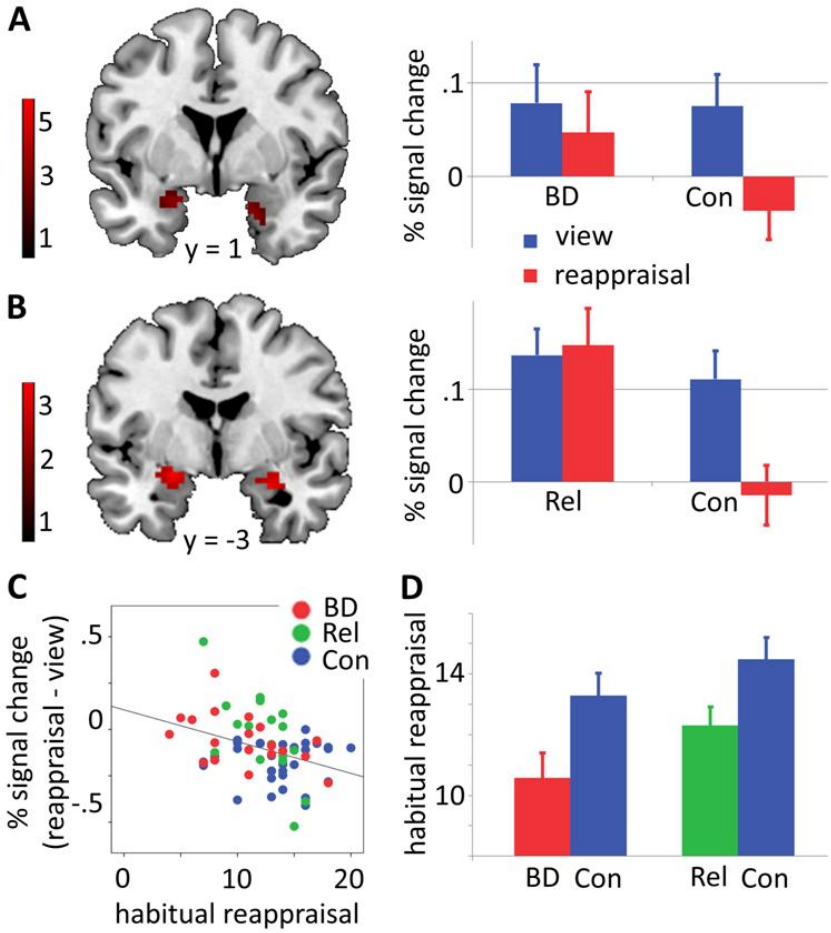
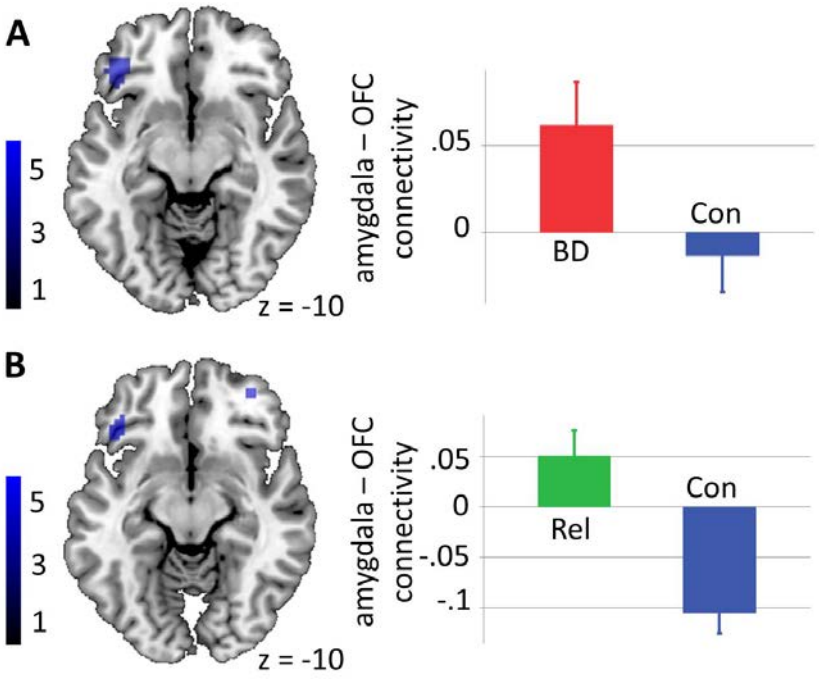

A
5
3
1
y = 1
% signal change
.1
0
BD
Con
view
reappraisal
B
3
2
1
y = -3
% signal change
.1
0
Rel
Con
C
% signal change
(reappraisal - view)
.5
0
-.5
BD
Rel
Con
0
10
20
habitual reappraisal
D
habitual reappraisal
14
10
BD Con
Rel Con

Figure 3


A
5
3
1
z = -10
amygdala – OFC connectivity
.05
0
BD
Con
B
5
3
1
z = -10
amygdala – OFC connectivity
.05
0
-.05
-.1
Rel
Con

Supplement S1: Mean valence and arousal ratings and standard deviations (in parentheses) for the selected pictures. Normative IAPS ratings and post-experimental ratings of BD patients (BD), their controls (BD-Con), and relatives (Rel) and their controls (Rel-Con)

	normative IAPS ratings		*BD ratings*		*BD-Con ratings*		*Rel ratings*		*Rel-Con ratings*	
	valence	arousal	valence	arousal	valence	arousal	valence	arousal	valence	arousal
Negative	1.87 (0.21)	6.28 (0.64)	2.11 (0.63)	5.78 (1.67)	2.72 (1.01)	5.58 (1.46)	2.82 (0.89)	4.65 (1.91)	2.74 (1.01)	5.22 (2.01)
Neutral	4.92 (0.28)	2.98 (0.34)	5.13 (0.70)	2.54 (1.64)	5.22 (0.34)	1.97 (1.22)	5.32 (0.54)	1.85 (1.12)	5.11 (0.17)	2.02 (1.18)
Positive	7.38 (0.39)	6.29 (0.68)	6.49 (1.26)	4.43 (1.72)	6.60 (0.90)	4.36 (1.42)	7.06 (0.72)	3.93 (1.56)	6.62 (0.96)	4.60 (1.79)

The post-experimental valence and arousal ratings of BD patients, relatives, and controls for the selected pictures were comparable to the normative IAPS ratings. Negative and positive pictures were rated as more arousing than neutral pictures (Sample 1: negative vs. neutral: $F(1,42) = 98.8$, $p<0.001$; positive vs. neutral: $F(1,42) = 90.4$, $p<0.001$, Sample 2: negative vs. neutral: $F(1,32) = 192.5$, $p<0.001$; positive vs. neutral: $F(1,32) = 116.7$, $p<0.001$). In addition, picture categories significantly differed regarding valence (positive > neutral > negative; Sample 1: $F(1,42) = 84.7$, $p<0.001$; $F(1,42) = 334.3$, $p<0.001$, Sample 2: $F(1,32) = 101.2$, $p<0.001$; $F(1,32) = 55.6$, $p<0.001$, respectively). There were no significant interactions with group or differences between groups (all $p>0.15$), except generally increased valence ratings in relatives compared to their controls (at trend-level, $F(1,32) = 3.8$, $p<0.10$) and to BD patients ($F(1,37) = 7.3$, $p<0.05$).

Supplement S2: Means and standard deviations (in parentheses) of the CERQ subscales in each group are displayed. Significant differences are marked with an asterisk

CERQ subscale	*BD*	*BD-Con*	*p*	*Rel*	*Rel-Con*	*p*	*BD vs. Rel p*
Self-blame	11.0 (3.6)	8.3 (1.8)	< .05*	7.7 (1.9)	8.4 (2.4)	> .10	< .05*
Blaming Others	6.9 (3.0)	6.2 (2.1)	> .10	6.5 (2.6)	5.9 (2.5)	> .10	> .10
Rumination	12.1 (3.9)	7.9 (2.7)	< .05*	7.7 (3.3)	7.8 (2.8)	> .10	< .05*
Catastrophizing	8.0 (3.2)	6.0 (1.7)	< .05*	5.9 (2.7)	6.1 (1.8)	> .10	< .05*
Putting into Perspective	12.2 (4.5)	13.5 (4.3)	> .10	13.4 (3.4)	14.2 (3.6)	> .10	> .10
Positive Refocusing	8.6 (3.7)	9.5 (3.5)	> .10	9.1 (3.6)	9.4 (3.1)	> .10	> .10
Positive Reappraisal	10.6 (3.9)	13.3 (3.5)	< .05*	12.3 (2.6)	14.5 (3.0)	< .05*	> .10
Acceptance	12.0 (3.0)	12.3 (4.1)	> .10	12.2 (4.3)	12.5 (3.2)	> .10	> .10
Refocus on Planning	10.4 (3.5)	11.6 (3.0)	> .10	12.1 (3.0)	12.5 (2.5)	> .10	> .10

Supplement S3: Activations in the different conditions across all participants

	H	BA	MNI coordinates			Cs	Z	T
			x	y	z			
view emotional - neutral								
amygdala	L		-21	-4	-14	26	3.65	3.85
	R		21	-1	-14	20	4.65	4.95
temporal/occipital	L	19	-42	-76	-2	1874	7.69	9.72
	R	19	51	-73	-2		7.39	9.18
posterior cingulate/precuneus	L	30	-3	-46	22	270	5.30	5.92
	R	23	3	-55	34		5.58	6.29
view emotional - reappraisal								
amygdala	L		-21	-7	-14	30	4.43	4.79
	R		21	-4	-17	56	5.25	5.85
occipital	L	19	-39	-76	4	237	5.67	6.43
	R	19	39	-82	1	511	5.68	6.44
ventral ACC	L	11	-9	38	-5	97	5.45	6.13
ventral temporal	R	30	12	-49	4	48	4.96	5.46
reapraisal - view emotional								
orbitofrontal	L	47	-48	32	-8	201	5.92	6.79
	R	47	51	35	-11	14	4.74	5.17
dorsomedial prefrontal	L	6	-9	8	64	395	6.19	7.20
inferior parietal / angular gyrus	L	39	-48	-67	46	471	7.02	8.52
	R	39	60	-55	34	286	6.88	8.28
precuneus	L	7	-6	-67	40	13	4.84	5.31
dorsolateral prefrontal	L	9	-45	14	46	238	6.05	6.98
middle temporal	L	21	-63	-37	-2	255	6.28	7.33
	R	21	57	-37	-2	71	5.18	5.75
view emotional - distraction								
amygdala	L	28	-24	-4	-23	68	>8.21	10.11
	R	20	27	-4	-20	69	7.60	9.56
ventromedial frontal / ACC	L	11	-3	35	-17	1393	>8.21	12.44
posterior cingulate	L	23	-3	-49	28	176	6.43	7.56
middle temporal	L	19	-54	-73	15	449	>8.21	10.23
	R	20	54	-7	-20	117	6.57	7.79
ventral temporal / occipital	R	19	54	-73	1	3826	>8.21	12.79
distraction - view emotional								
superior parietal	L	7	-27	-61	43	3273	>8.21	14.20
	R	40	42	-46	43		>8.21	12.07
dorsomedial prefrontal / ACC	L	32	-6	11	49	4633	>8.21	12.28
	R	32	6	20	46		>8.21	10.31
insula	L	48	-30	20	4		>8.21	9.45
	R	48	35	20	4		>8.21	10.95
dorsolateral prefrontal	L	45	-45	29	28		>8.21	9.54
	R	46	39	38	22		>8.21	9.64
cerebellum	R	37	18	-49	-26	185	6.30	7.36
inferior temporal	L	37	-54	-58	-14	87	7.14	8.73
	R	20	57	-46	-14	19	5.43	6.09
occipital	L	18	-24	-97	-5	191	6.78	8.12
	R	17	24	-100	-2	62	5.12	5.68

H = Hemisphere; BA = Brodmann area of the peak activation; CS = Cluster size in number of activated voxels; if no CS is given, the activation peak belongs to the cluster listed directly above

Supplement S4: Task difficulty and effort ratings

Directly after the experiment, participants rated the difficulty and effort required for each experimental condition, to ensure that different results for reappraisal and distraction were not due to differences in task difficulty. Across BD patients and matched controls, the ratings yielded no significant differences between conditions and no interactions with group (all $p>0.65$). Due to a technical problem the ratings of some of the control participants matched to the unaffected relatives were not recorded, but comparing relatives to BD patients yielded also no significant differences or interactions (all $p>0.70$).

5.2 Neural correlates of emotional distractibility in healthy participants, euthymic patients with bipolar disorder, unaffected relatives of bipolar patients and healthy individuals with hypomanic personality

This section presents two studies investigating the influence of emotion on cognitive processing. The first study describes a two-step experimental procedure to show the effect of emotionally salient stimuli on a specific cognitive capability, namely mental arithmetic processing. This study was done in healthy control participants. The second study applied this procedure to euthymic patients with bipolar disorder and to two groups of healthy participants at high risk to develop bipolar disorder, unaffected relatives of bipolar patients and healthy individuals with hypomanic personality.

- Wessa, M., Heissler, J., Schönfelder, S., **Kanske, P.** (2013). Goal-directed behavior under emotional distraction is preserved by enhanced task-specific activation. *Social Cognitive and Affective Neuroscience*, *8*, 305-12.
- **Kanske, P.**, Heissler, J. ,Schönfelder, S., Forneck, J., Wessa, M. (2013). Neural correlates of emotional distractibility in bipolar disorder, unaffected relatives and individuals with hypomanic personality. *American Journal of Psychiatry 170*, 1487-1496.

doi:10.1093/scan/nsr098 SCAN (2013) 8, 305–312

Goal-directed behavior under emotional distraction is preserved by enhanced task-specific activation

Michèle Wessa,[1,2] Janine Heissler,[1,3] Sandra Schönfelder,[1,2] and Philipp Kanske[1,2]

[1]Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, 68159 Mannheim, Germany, [2]Section for Experimental Psychopathology and Neuroimaging, Department of General Psychiatry, Center for Psychosocial Medicine, Heidelberg University, 69115 Heidelberg, Germany and [3]Center for Doctoral Studies in Social and Behavioral Sciences, Graduate School of Economic and Social Sciences, University of Mannheim, 68161 Mannheim, Germany

Despite the distracting effects of emotional stimuli on concurrent task performance, humans are able to uphold goal-directed behavior. Here, we investigated the hypothesis that this effect is due to the enhanced recruitment of task-specific neural resources. In a two-step functional magnetic resonance imaging study, we first localized those areas involved in mental arithmetics by contrasting arithmetic problems with a number detection task. The resulting activation maps were then used as masks in a second experiment that compared the effects of neutral and emotional distracter images on mental arithmetics. We found increased response times in the emotional distracter condition, accompanied by enhanced activation in task-specific areas, including superior parietal cortex, dorsolateral and dorsomedial prefrontal cortex. This activation increase correlated with larger behavioral impairment through emotional distraction. Similar error rates in both conditions indicate that cognitive task performance is preserved through enhanced recruitment of task-specific neural resources when emotional distracter stimuli are present.

Keywords: affect; emotion; cognition; arithmetic; fMRI

INTRODUCTION

Even in the presence of distracting stimuli, humans are able to coherently perform cognitive tasks such as working memory functions or mental arithmetics. Emotional stimuli are particularly salient distracters. They signal potentially threatening or rewarding events and are thought to automatically attract attentional resources. A large body of research studied the question of whether and how emotional stimuli are automatically detected even under conditions of high cognitive load (Pessoa *et al.*, 2002; Erk *et al.*, 2007; Van Dillen *et al.*, 2009). These studies suggest that performing cognitive tasks reduces detection rates of emotional stimuli and emotion-related activity, for example in the amygdala. In contrast, we know less about the effects that emotional distracters have on cognitive task performance. Evidence from different cognitive tasks suggests that task performance is impaired when emotional stimuli are presented as distracters before (Pereira *et al.*, 2010) or during the task (Vuilleumier *et al.*, 2001). But these effects are rather small and rarely affect accuracy of performance. Thus, a critical question is how task performance is secured in situations of emotional distraction. One hypothesis is that more neural resources are devoted to task performance. In line with this suggestion, a few studies found increased activation in task-relevant brain regions, potentially indicating compensatory activation to preserve goal-directed behavior (Blair *et al.*, 2007; Hart *et al.*, 2010; Pereira *et al.*, 2010). A number of other studies, however, found a reduction of task-relevant activations, which was interpreted as emotion taking the cognitive processing system 'off-line' (Dolcos and McCarthy, 2006; Dolcos *et al.*, 2006; Mitchell *et al.*, 2008; Anticevic *et al.*, 2010). This discrepancy has not yet been solved, but might be due to one shortcoming of the described studies. They did not directly test if the hyper- and hypo-activations were really located in brain regions that are essential and specific for processing the task. It may thus be that the observed effect was not directly related to the task, but to another concurrent process. Therefore, we targeted the question with a two-step fMRI experiment. We first localized brain regions involved in mental arithmetics by directly contrasting an arithmetic task with a number detection task (see, e.g. Rickard *et al.*, 2000). In line with previous studies, we expected this task to yield activation in bilateral parietal cortex and potentially also in dorsolateral and dorsomedial prefrontal cortex (Menon *et al.*, 2000b; Ischebeck *et al.*, 2009). We then used these activation clusters to mask the results of a second experiment in which participants performed arithmetic tasks presented on emotional and neutral distracter images. In contrast to previous studies, this ensures that

Received 8 July 2011; Accepted 20 December 2011
Advance Access publication 1 February 2012
We wish to thank Heike Schmidt for help with the data acquisition. This research was funded by the Deutsche Forschungsgemeinschaft (grant We3638/3-1).

Correspondence should be addressed to Philipp Kanske, PhD, Section for Experimental Psychopathology and Neuroimaging, Department of General Psychiatry, Center for Psychosocial Medicine, University of Heidelberg, Vossstr. 4, 69115 Heidelberg, Germany. E-mail: philipp.kanske@med.uni-heidelberg.de

the analyzed effect of emotional distraction on task processing really includes task-specific brain regions. If the hypothesis, that task performance is upheld by the recruitment of more neural resources is correct, then activation in these regions should be enhanced under emotional distraction, particularly in participants who show high behavioral interference effects.

MATERIALS AND METHODS

Participants

Thirty healthy volunteers (17 female, aged 18–27 years, mean age 21.8 ± 2.1 years) participated in the study. Twenty-six participants were right-handed, four participants were left-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). All participants had normal or corrected-to-normal vision and were medically healthy, reported no history of mental disorders as verified by the Structured Clinical Interview for DSM-IV (SCID-I and -II; German version: Wittchen *et al.*, 1997), no history of serious head injury, neurological disorder or dyscalculia. The Ethics Committee of the University of Heidelberg approved the study and all participants gave written informed consent prior to participation.

Experimental paradigm and procedure

Two experimental tasks were presented (Figure 1). The first was a localizer to identify brain activation specific to the mental arithmetic operations of addition and subtraction. Therefore, 20 arithmetic problems (e.g. 8 − 3 + 7 = 12) and 20 rows of numbers (e.g. 4 11 0 7) were presented for 6 s each. Participants decided whether the presented solution for the equation was correct or incorrect, and whether a '0' was part of the rows of numbers or not. As soon as participants pressed a button, a thin white frame line was presented around the numbers. All trials were presented in pseudo-randomized order. The task lasted ∼8 min.

The second task presented arithmetic problems equivalent to, but different from the localizer task, superimposed on neutral and emotional pictures. The pictures were also presented without an arithmetic task and another condition required participants to reappraise the contents of the images to reduce the elicited emotion; the results of these conditions were presented elsewhere (Kanske *et al.*, 2011). Each trial started with a fixation cross presented with a jitter of 3000–5025 ms and followed by (i) an emotion induction phase (1000 ms), (ii) the distraction (i.e. the presentation of an arithmetic problem; 6000 ms) and (iii) a rating phase (which is not relevant for the present paper; 4000 ms). During the induction phase, participants passively viewed pictures to elicit an initial emotional response. The arithmetic problem was then presented for 6000 ms as a transparent overlay on the picture. As soon as participants pressed a button, a thin white frame line was presented around the overlay.

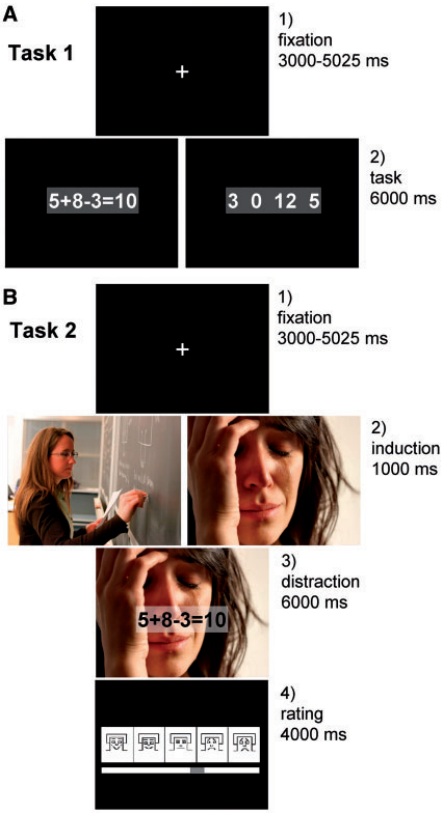


Fig. 1 Sequence of events in a trial of the localizer (**A**) and the experimental task (**B**). The example pictures resemble those in the experiment, but are not part of the IAPS.

The experiment consisted of 128 trials, which were presented in a pseudo-randomized order and lasted ∼35 min. Participants received six training trials prior to the experiment, to familiarize them with the procedure.

Stimuli

Pictures were selected from the International Affective Picture System (IAPS; Lang *et al.*, 2005). Sets of 16 highly arousing, negative, 16 neutral, low in arousal and 16 highly arousing, positive stimuli, were created (see Table 1 for mean ratings). An ANOVA confirmed the selection, showing significant effects of picture category on valence and arousal ratings [$F(2,45) = 1332.84$, $P < 0.001$ and $F(2, 45) = 176.65$, $P < 0.001$, respectively]. Differences in valence ratings were observed for each category (all $P < 0.001$), while arousal ratings did not differ for positive *vs* negative, but for emotional *vs* neutral stimuli ($P < 0.001$). To assess whether the participants of the present study evaluated the stimuli similarly to the IAPS normative sample, we had each participant rate

Table 1 Mean valence and arousal ratings and s.d.'s (in parentheses) for the picture selection

	Normative IAPS ratings		Sample ratings	
	Valence	Arousal	Valence	Arousal
Negative	1.87 (0.21)	6.28 (0.64)	2.48 (0.49)	6.00 (1.00)
Neutral	4.92 (0.28)	2.98 (0.34)	5.19 (0.42)	1.77 (0.35)
Positive	7.38 (0.39)	6.29 (0.68)	7.21 (0.35)	5.16 (0.60)

Normative IAPS ratings and the ratings of the present sample are displayed.

each image again after the scanner experiment. To ensure that these ratings were unaffected by the experimental procedures, we did not use the rating phase of the main experiment for the valence values, but conducted the rating after the experiment outside the scanner. The rating was done on a 9-point scale using the Self-Assessment Manikins (Bradley and Lang, 1994). Participants pressed one of nine buttons, each corresponding to one point on the scale (ranging from low to high arousal, and negative to positive valence). The results were comparable to the normative IAPS ratings, but differed in arousal ratings for the positive pictures, which were rated less arousing than negative pictures (see Table 1; $P < 0.001$).

All arithmetic problems were formed with three operands including a subtraction and an addition (e.g. $4 + 9 - 6 = 7$). Initially, 130 arithmetic problems were tested in an independent sample of 10 healthy participants. From these, 20 equations were selected for the localizer task and 48 equations were selected for the main experiment such that they were correctly solved by at least 75% of the sample. These selected equations were randomly assigned to the background picture condition (negative, neutral, positive) such that there were no differences in RTs or number of errors based on the data of the pilot sample (all $P > 0.25$). For the number detection task in the localizer task, the set of numbers contained as many numbers as the arithmetic problems, only the operands were missing. Thus, visual input was kept almost identical.

MRI data acquisition

MRI data were collected on a 3T scanner (Magnetom TIM Trio, Siemens Medical Solutions, Erlangen, Germany) at the Central Institute of Mental Health, Mannheim. A high-resolution T1-weighted 3D image was acquired (slice thickness = 1.1 mm, FOV = 256 mm × 256 mm × 256 mm, matrix = 256 × 256 × 256). Functional images were obtained from 40 gradient-echo T2*-weighted slices (slice thickness = 2.3 mm) per volume. A single-shot echo-planar sequence with parallel imaging GRAPPA technique (acceleration factor 2) was used with a TR of 2700 ms, a flip angle of 90°, TE = 27 ms, FOV = 220 mm × 220 mm, matrix = 96 × 96 and a slice gap of 0.7 mm.

fMRI data analysis

Image processing and statistical analysis was done with SPM5 (http://www.fil.ion.ucl.ac.uk/). Functional images were realigned, slice-time corrected and spatially normalized using the Montreal Neurological Institute (MNI) template. For normalization, images were resampled every 3 mm using sinc interpolation. Images were smoothed using a 9 mm × 9 mm × 9 mm Gaussian kernel.

Individual participants' data were analyzed using a General Linear Model for blood oxygen level-dependant (BOLD) signal changes due to the experimental conditions. Movement parameters calculated during realignment were included as parameters of no interest to control for movement artifacts. Individual statistical parametric maps were calculated for the contrasts of interest in order to investigate BOLD signal changes to (i) mental arithmetics (localizer task: arithmetic problems—number detection) and (ii) the influence of emotion on mental arithmetics (main task: arithmetic problems superimposed on emotional—neutral pictures). In a first step, the analyses were done for positive and negative emotional stimuli separately, which yielded largely comparable results. Also, directly comparing the two emotional categories only yielded stronger activation for negative stimuli in the bilateral ventral temporal cortex (see Supplement S1 in Supplementary Data), which is not part of the mental arithmetics network. To enhance statistical power, we thus pooled positive and negative stimuli, creating one emotional condition for the analyses reported here.

Second-level random-effects analyses were calculated. One-sample *t*-tests were computed on the above mentioned individual contrast images. Activations were thresholded at a whole-brain FDR corrected $P < 0.05$ with an extent threshold of 20 voxels in order to protect against false-positive activations. From the activations found in the localizer task, a mask image was created using the same thresholds. This mask was then used for the main task, which was thresholded again.

RESULTS

Behavioral results

Localizer task

Accuracy was higher for the number detection compared to the arithmetic task [$M = 96.2\%$, s.d. = 12.0; $M = 76.8\%$, s.d. = 18.1; $F(1,29) = 30.3$, $P < 0.001$]. Reaction times to number detection were also shorter than to the arithmetic tasks [see Figure 2D; $M = 1.2$ s, s.d. = 0.6; $M = 3.7$ s, s.d. = 0.5; $F(1,29) = 486.5$, $P < 0.001$].

Main task

As there were no significant differences between reaction times in positive and negative trials, these were averaged to an emotional condition [negative: $M = 3.55$ s, s.d. = 0.50; positive: $M = 3.51$ s, s.d. = 0.52; $F(1,29) = 0.2$, $P > 0.60$]. Reaction times were longer for this emotional compared to

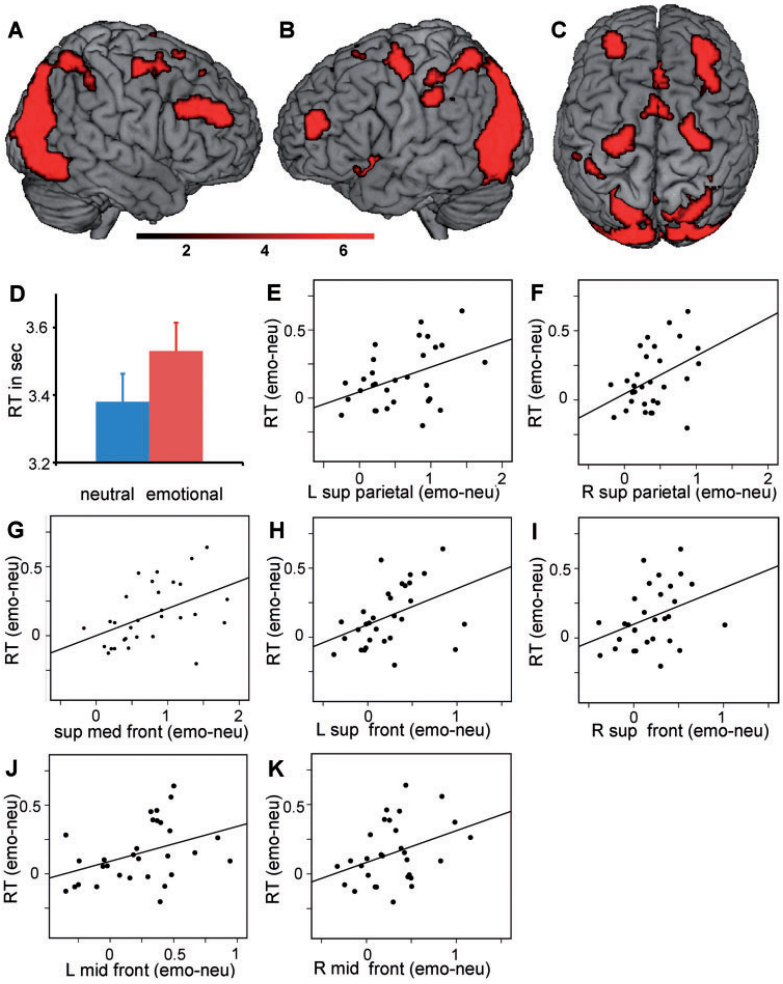


Fig. 2 Activations for mental arithmetics on emotional *vs* neutral distracters in viewed from the right (**A**) and the left side (**B**) and from above (**C**). Reaction times in the experimental task (**D**) and correlations of the reaction time difference and activation differences between emotional and neutral trials in left (**E**) and right (**F**) superior parietal cortex, superior medial frontal cortex (**G**), left (**H**) and right (**I**) superior frontal, and left (**J**) and right (**K**) middle frontal cortex.

neutral distracter trials [see Figure 2; neutral: $M = 3.38$ s, s.d. $= 0.45$; emotional: $M = 3.53$ s, s.d. $= 0.46$; $F(1,29) = 14.1$, $P < 0.001$]. Arithmetic problems (90.8%) were correctly solved (s.d. 6.2), there were no significant differences between conditions [$F(1,29) = 0.6$, $P > 0.45$].

fMRI results

Localizer task

The contrast of arithmetic tasks with the number detection tasks in the localizer yielded activation in widespread network of brain regions including the parietal cortex, lateral and medial prefrontal cortex, and the insula (Table 2).

Main task

The activation clusters identified in the localizer task were used as masks for the contrast of arithmetic problems presented on emotional and neutral distracters. We observed no significant activation for the neutral over the emotional distracter condition (even with a more lenient threshold of $P < 0.001$ uncorrected, and also when conducting a whole-brain analysis). However, the parietal cortex, regions in the lateral prefrontal cortex and the left insula were activated more strongly for mental arithmetics in emotional when compared to neutral distracter trials (Table 2 and Figure 2).

Table 2 Peak activations in the localizer and main task for mental arithmetics and mental arithmetics on emotional *vs* neutral distracters

	H	BA	MNI coordinates			CS	*Z*
			x	*y*	*z*		
Arithmetic—number detection							
Superior frontal	L	6/8	−27	0	60	1092	6.40
Middle frontal	L	10/45/46	−36	54	15	[a]	5.79
Superior frontal	R	6/8	30	3	57	1164	5.90
Middle frontal	R	10/45/46	45	42	27	[a]	5.51
Medial frontal/anterior cingulated	R	6/8/24/32	6	18	51	425	7.24
Insula	L	6/8/24/32	−6	15	45	[a]	6.64
	R	48	36	21	−3	265	7.46
	L	48	−33	21	−3	230	7.43
Inferior parietal	L	40	−42	−39	42	2941	7.63
Superior parietal	L	7	−24	−59	39	[a]	7.30
Inferior parietal	R	40	45	−39	45	[a]	6.64
Superior parietal	R	7/40	33	−48	45	[a]	6.91
Middle occipital	L	17/18/19	−33	−84	12	[a]	7.19
	R	17/18/19	30	−96	3	[a]	6.82
Arithmetic emotional—arithmetic neutral							
Superior frontal	L	6	−21	−6	72	133	3.19
Middle frontal	L	46	−30	−54	24	57	3.54
Superior frontal	R	6	21	0	55	104	3.90
Middle frontal	R	46	30	51	27	122	3.99
Superior medial frontal	L	8/32	−3	18	44	72	2.79
Anterior cingulated	R	24/32	6	39	27	63	3.16
	L	24/32	−5	33	27	[a]	3.05
Insula	L	48	−27	15	−14	37	3.87
Middle occipital	L	17/18/19	−42	−81	12	4396	5.50
	R	17/18/19	30	−75	30	[a]	5.17
Superior parietal	R	7/40	24	−60	63	[a]	3.16
	L	7/40	−18	−60	60	[a]	4.06

[a]Indicates that this peak is part of the cluster listed earlier.
H = Hemisphere; CS = Cluster size in number of activated voxels.

Correlations

To further assess the relation of the increased task-related activation under emotional distraction to the behavioral distraction effect, we conducted a correlational analysis. We extracted the first eigenvariate of the time-course of the activations in Table 2 with a spherical 5-mm radius ROI and correlated it to the RT difference between emotional and neutral trials (Table 3). This yielded significant correlations with left and right superior parietal cortex, superior medial frontal cortex, as well as left and right middle and superior frontal cortex. The data indicate that larger behavioral interference was accompanied by increased activation in the respective brain regions. To assess the specificity of these correlations to task-related processing, we also calculated correlations with activity in the left and right amygdala, which we had found to be active when comparing emotional with neutral images in a simple viewing condition (Kanske *et al.*, 2011), but which was not part of the network for arithmetic processing as identified in the localizer task. For this analysis, we extracted the first eigenvariate for the present contrast (arithmetic tasks on emotional *vs* neutral background images) from 5 mm spheres defined by the amygdala

Table 3 Correlations of the activations observed in the contrast of 'arithmetic emotional—arithmetic neutral' (Table 2) with the behavioral distraction effect, i.e. RTs emotional—neutral

	H	*r*	*P*
Superior frontal	L	0.42	0.010*
	R	0.37	0.023*
Middle frontal	L	0.39	0.016*
	R	0.37	0.023*
Superior medial frontal	L	0.47	0.005**
Anterior cingulated	R	0.01	0.463
	L	0.14	0.217
Insula	L	0.25	0.090
Middle occipital	L	0.01	0.487
	R	0.29	0.061
Superior parietal	R	0.41	0.010*
	L	0.42	0.013*
Amygdale	L	0.19	0.149
	R	−0.03	0.426

Additionally, the correlation of the RT effect with left and right amygdala activity extracted from the same contrast, but without the localizer mask, is reported.
H = Hemisphere, *r* = Pearson correlation coefficient, $^{*}P < 0.05$, $^{**}P < 0.01$.

activation, we had found when contrasting emotional and neutral stimuli in a simple viewing condition in which participants attended to the images, but performed no parallel task (see Kanske *et al.*, 2011). Here, we found no significant correlation (Table 3).

DISCUSSION

The present study gives new insights into the effects of emotional distraction on cognitive task performance. Emotional background images increased response times, but did not affect error rates, indicating that emotion did have a distracting effect, but that participants were still able to uphold goal-directed behavior. This effect was accompanied by increased activation for mental arithmetics in task-specific brain regions. This increase was particularly strong in participants showing larger behavioral interference. The data suggest that it is enhanced recruitment of task-specific neural resources that ensures continued task performance even when emotional distracters are present.

Thereby, the present results clarify previous data with inconsistent effects of emotional distraction on cognitive tasks. While some studies found enhanced activation in dorsal 'cognitive' brain regions (Blair *et al.*, 2007; Hart *et al.*, 2010; Pereira *et al.*, 2010), others reported an activation decrease in these areas (Dolcos and McCarthy, 2006; Dolcos *et al.*, 2006; Mitchell *et al.*, 2008; Anticevic *et al.*, 2010). The present study differs from previous approaches in the direct localization of task-specific brain regions, before measuring the distraction effects in these areas. As our data show enhanced activations under emotional distraction, they conform to the hypothesis that task-specific activation is boosted in order to overcome the distraction effect. This suggests that the activation reduction found in some studies is not directly task-related, but reflects some other cognitive process. The exact nature of this process is unclear, however, one putative role is the inhibition of task-irrelevant information and the protection against interference (Shimamura, 2000; Jha *et al.*, 2004). A study by Sommer *et al.* (2008) hints at that. The authors used a spatial conflict paradigm in which the shape of a stimulus determined the response, while the stimulus location elicited an interfering response tendency in some trials. Here, emotion caused disturbed behavioral conflict resolution along with reduced dlPFC and ACC activation. Future studies should target this question, possibly by combining conflict paradigms with the present approach.

The results differ markedly from previous reports of facilitated cognitive task performance induced by emotional stimuli, for example, of attention (Keil *et al.*, 2005) or cognitive control (Kanske and Kotz, 2011b). This discrepancy is best explained by the role of the emotional stimuli in the respective tasks. While they were not behaviorally relevant and presented in the background of the target stimuli in the present study, facilitation effects are observed when the task-specific target stimuli themselves are emotional. Interestingly, this emotional facilitation is accompanied by increased activation in brain regions involved in the processing of conflict (Kanske and Kotz, 2011a), which complements the data by Sommer *et al.* (2008) discussed earlier.

An alternative explanation for the present results is that the observed hyper-activation directly reflects emotional processing and not the effect of emotion on task-performance. However, this possibility is highly unlikely. First, the results were masked with the activation clusters found for arithmetic processing in the localizer task. This task did not involve emotional stimuli, the resulting mask image should therefore not include emotion specific activations. Second, contrasting emotional with neutral stimuli without specific task demands activates a more ventral–limbic network that does not overlap with the task-related activations reported here (Kanske *et al.*, 2011). Furthermore, the correlation of the activation increase with the RT interference effect may also suggest that the observed areas are directly relevant for task performance. Even though it is principally possible that increased behavioral interference is related to enhanced activity in emotion-related brain regions, the lack of a significant correlation between RTs and amygdala activity suggests otherwise. The amygdala was found to be active when contrasting emotional and neutral images in a simple viewing condition without any active task superimposed (Kanske *et al.*, 2011), but not in the arithmetic localizer task, which demonstrates its involvement in emotional, rather than cognitive processing. As the correlations between behavior and brain activity were restricted to regions activated in the localizer task, this correlation seems to be specific for task-related activation.

Interestingly, significant correlations were not observed across all of the observed activations, but only in superior parietal, superior and middle frontal and superior medial frontal cortex. These regions are those most consistently found in studies on arithmetic processing, in particular parietal and middle prefrontal cortex have been described as hosting representations of quantity and mental calculation (for a review, see Dehaene *et al.*, 2004). It is, therefore, possible that while activity in a larger task-related network is enhanced to overcome emotional distraction effects and ensure correct task performance, only those regions directly involved in arithmetic operations show a relation to increased RTs during distraction. According to Perneger (1998), we did not correct the correlations for multiple comparisons. Testing the whole pattern of correlations between the RT and fMRI data provides more and very specific information, for example, by including the amygdala activity, for which we expected no significant effects (see also Hensch *et al.*, 2007). To allow an evaluation of the psychological importance of the results, we report the exact *P*-values along with the correlations (as standardized effect sizes) as recommended by Nakagawa (2004).

One limitation of the present study concerns the question how specific the neural network that was identified in the

localizer task is for arithmetic processing. Because of lower accuracy and longer RTs, task difficulty seems to have been higher in the arithmetic compared to the number detection task. It is therefore possible that some of the observed activations are due to task difficulty and not mental arithmetics. This argument applies to a number of previous studies on arithmetic processing that also used number detection as control conditions (Menon *et al.*, 2000a, 2000b; Rickard *et al.*, 2000). Nevertheless, the neural network identified for arithmetic processing across different types of tasks including a variety of different control conditions is largely overlapping and corresponds well to the clusters observed in the present study (Fehr *et al.*, 2007; Grabner *et al.*, 2007; Zago *et al.*, 2008; Ischebeck *et al.*, 2009). This suggests that there is some functional specificity for arithmetic processing in the network. Future studies should validate this point, potentially using the conjunct activity of different tasks as mask images. In a similar vein, as the results were masked it seems odd that we observed activation in the insula, which has been mainly implicated in emotional processing (Singer *et al.*, 2009). However, insula activation is also a common finding in studies of arithmetic processing (Menon *et al.*, 2000b; Grabner *et al.*, 2007, 2009; Ischebeck *et al.*, 2009) and was also part of the network identified in the localizer task. The arithmetic activation seems to be slightly anterior to the emotional activation (see also Kanske *et al.*, 2011), but the exact role of the insula in mental arithmetics still needs to be elucidated.

A second limitation concerns the differentiation of the emotional distraction effects. We observed no relevant differences in behavior and neural activity between positive and negative images, which could suggest that it is mainly the increased arousal in the emotional conditions that drives the distraction effects. This could be tested in future studies by systematically manipulating valence and arousal values of the presented stimuli. Furthermore, it is conceivable that the distraction effects may vary for different emotions such as anger, fear or joy (for a meta-analysis on commonalities and differences in the neural underpinnings of different emotions see Phan *et al.*, 2002), which is also an empirical question for future studies.

The present data are also relevant for the interpretation of previous results from patients with mental disorders. Despite preserved behavioral task performance, patients with depression or bipolar disorder, for example, show enhanced task-related activity under emotional distraction (Wessa *et al.*, 2007; Dichter *et al.*, 2009). Our data support the authors' interpretation of these effects as a compensatory mechanism to deal with greater emotional interference, which may be caused by hyper-activation in limbic regions involved in affective processing (Phillips *et al.*, 2008).

To conclude, the present study showed that task performance under emotional distraction is preserved through enhanced activation in task-specific brain regions. The use of a two-step fMRI procedure, which first localized task-related activations before investigating the effect of emotion on them, was fruitful and is recommended for future studies.

SUPPLEMENTARY DATA

Supplementary Data are available at *SCAN* online.

Conflict of Interest

None declared.

REFERENCES

Anticevic, A., Repovs, G., Barch, D.M. (2010). Resisting emotional interference: brain regions facilitating working memory performance during negative distraction. *Cognitive, Affective & Behavioral Neuroscience*, *10*, 159–73.

Blair, K.S., Smith, B.W., Mitchell, D.G., et al. (2007). Modulation of emotion by cognition and cognition by emotion. *Neuroimage*, *35*, 430–40.

Bradley, M.M., Lang, P.J. (1994). Measuring emotion: the self-assessment manikin and the semantic differential. *Journal of Behavioral Therary and Experimental Psychiatry*, *25*, 49–59.

Dehaene, S., Molko, N., Cohen, L., Wilson, A.J. (2004). Arithmetic and the brain. *Current Opinion in Neurobiology*, *14*, 218–24.

Dichter, G.S., Felder, J.N., Smoski, M.J. (2009). Affective context interferes with cognitive control in unipolar depression: an fMRI investigation. *Journal of Affective Disorder*, *114*, 131–42.

Dolcos, F., Kragel, P., Wang, L., McCarthy, G. (2006). Role of the inferior frontal cortex in coping with distracting emotions. *Neuroreport*, *17*, 1591–4.

Dolcos, F., McCarthy, G. (2006). Brain systems mediating cognitive interference by emotional distraction. *Journal of Neuroscience*, *26*, 2072–9.

Erk, S., Kleczar, A., Walter, H. (2007). Valence-specific regulation effects in a working memory task with emotional context. *Neuroimage*, *37*, 623–2.

Fehr, T., Code, C., Herrmann, M. (2007). Common brain regions underlying different arithmetic operations as revealed by conjunct fMRI-BOLD activation. *Brain Research*, *1172*, 93–102.

Grabner, R.H., Ansari, D., Koschutnig, K., Reishofer, G., Ebner, F., Neuper, C. (2009). To retrieve or to calculate? Left angular gyrus mediates the retrieval of arithmetic facts during problem solving. *Neuropsychologia*, *47*, 604–8.

Grabner, R.H., Ansari, D., Reishofer, G., Stern, E., Ebner, F., Neuper, C. (2007). Individual differences in mathematical competence predict parietal brain activation during mental calculation. *Neuroimage*, *38*, 346–56.

Hart, S.J., Green, S.R., Casp, M., Belger, A. (2010). Emotional priming effects during Stroop task performance. *Neuroimage*, *49*, 2662–70.

Hensch, T., Herold, U., Brocke, B. (2007). An electrophysiological endophenotype of hypomanic and hyperthymic personality. *Journal of Affective Disorder*, *101*, 13–26.

Ischebeck, A., Zamarian, L., Schocke, M., Delazer, M. (2009). Flexible transfer of knowledge in mental arithmetic–an fMRI study. *Neuroimage*, *44*, 1103–12.

Jha, A.P., Fabian, S.A., Aguirre, G.K. (2004). The role of prefrontal cortex in resolving distractor interference. *Cognitive, Affective & Behavioral Neuroscience*, *4*, 517–27.

Kanske, P., Heissler, J., Schonfelder, S., Bongers, A., Wessa, M. (2011). How to regulate emotion? Neural networks for reappraisal and distraction. *Cerebral Cortex*, *21*, 1379–88.

Kanske, P., Kotz, S.A. (2011a). Emotion speeds up conflict resolution: a new role for the ventral anterior cingulate cortex? *Cerebral Cortex*, *21*, 911–9.

Kanske, P., Kotz, S.A. (2011b). Emotion triggers executive attention: anterior cingulate cortex and amygdala responses to emotional words in a conflict task. *Human Brain Mapping*, *32*, 198–208.

Keil, A., Moratti, S., Sabatinelli, D., Bradley, M.M., Lang, P.J. (2005). Additive effects of emotional content and spatial selective attention on electrocortical facilitation. *Cerebral Cortex*, *15*, 1187–97.

Lang, P.J., Bradley, M.M., Cuthbert, B.N. (2005). *International Affective Picture System (IAPS): Affective Ratings of Pictures and Instruction Manual. Technical Report A-6*. Gainesville, FL: Center for Research in Psychophysiology, University of Florida.

Menon, V., Rivera, S.M., White, C.D., Eliez, S., Glover, G.H., Reiss, A.L. (2000a). Functional optimization of arithmetic processing in perfect performers. *Brain Research: Cognition Brain Research*, *9*, 343–5.

Menon, V., Rivera, S.M., White, C.D., Glover, G.H., Reiss, A.L. (2000b). Dissociating prefrontal and parietal cortex activation during arithmetic processing. *Neuroimage*, *12*, 357–65.

Mitchell, D.G., Luo, Q., Mondillo, K., Vythilingam, M., Finger, E.C., Blair, R.J. (2008). The interference of operant task performance by emotional distracters: an antagonistic relationship between the amygdala and frontoparietal cortices. *Neuroimage*, *40*, 859–68.

Nakagawa, S. (2004). A farewell to Bonferroni: the problems of low statistical power and publication bias. *Behavioral Ecology*, *15*, 1044–5.

Oldfield, R.C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*, *9*, 97–113.

Pereira, M.G., de Oliveira, L., Erthal, F.S., et al. (2010). Emotion affects action: midcingulate cortex as a pivotal node of interaction between negative emotion and motor signals. *Cogniitve, Affectine & Behavioral Neuroscience*, *10*, 94–106.

Perneger, T.V. (1998). What's wrong with Bonferroni adjustments. *BMJ*, *316*, 1236–8.

Pessoa, L., McKenna, M., Gutierrez, E., Ungerleider, L.G. (2002). Neural processing of emotional faces requires attention. *Proceedings of the National Academy of Science in United States of America*, *99*, 11458–63.

Phan, K.L., Wager, T., Taylor, S.F., Liberzon, I. (2002). Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage*, *16*, 331–48.

Phillips, M.L., Ladouceur, C.D., Drevets, W.C. (2008). A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. *Molecular Psychiatry*, *13*, 829, 833–57.

Rickard, T.C., Romero, S.G., Basso, G., Wharton, C., Flitman, S., Grafman, J. (2000). The calculating brain: an fMRI study. *Neuropsychologia*, *38*, 325–35.

Shimamura, A.P. (2000). The role of the prefrontal cortex in dynamic filtering. *Psychobiology*, *28*, 207–18.

Singer, T., Critchley, H.D., Preuschoff, K. (2009). A common role of insula in feelings, empathy and uncertainty. *Trends in Cognitive Sciences*, *13*, 334–40.

Sommer, M., Hajak, G., Dohnel, K., Meinhardt, J., Muller, J.L. (2008). Emotion-dependent modulation of interference processes: an fMRI study. *Acta Neurobiologine Experimentalis*, *68*, 193–203.

Van Dillen, L.F., Heslenfeld, D.J., Koole, S.L. (2009). Tuning down the emotional brain: an fMRI study of the effects of cognitive load on the processing of affective images. *Neuroimage*, *45*, 1212–9.

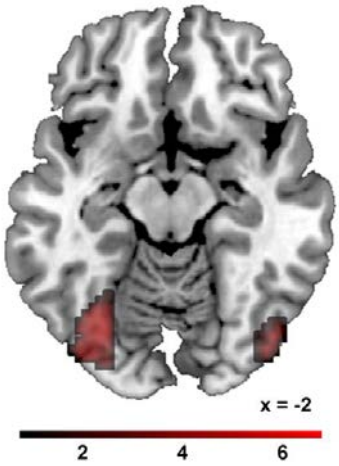
Vuilleumier, P., Armony, J.L., Driver, J., Dolan, R.J. (2001). Effects of attention and emotion on face processing in the human brain: an event-related fMRI study. *Neuron*, *30*, 829–41.

Wessa, M., Houenou, J., Paillere-Martinot, M.L., et al. (2007). Fronto-striatal overactivation in euthymic bipolar patients during an emotional go/nogo task. *American Journal of Psychiatry*, *164*, 638–46.

Wittchen, H.-U., Zaudig, M., Fydrich, T. (1997). *SKID-I. Strukturiertes Klinisches Interview für DSM-IV [Structural Clinical Interview for DSM-IV Axis I Disorders]*. Göttingen: Hogrefe.

Zago, L., Petit, L., Turbelin, M.R., Andersson, F., Vigneau, M., Tzourio-Mazoyer, N. (2008). How verbal and spatial manipulation networks contribute to calculation: an fMRI study. *Neuropsychologia*, *46*, 2403–14.

Supplement 1



Regions in the bilateral ventral temporal cortex activated for negative compared to positive stimuli. The activation peaks were found in the left (x = -27, y = -72, z = -12, CS = 370, Z = 4.23) and right fusiform gyrus (x = 42, y = -78, z = -15, CS = 30, Z = 4.35).

Article

Neural Correlates of Emotional Distractibility in Bipolar Disorder Patients, Unaffected Relatives, and Individuals With Hypomanic Personality

Philipp Kanske, Ph.D.

Janine Heissler, Ph.D.

Sandra Schönfelder, M.Sc.

Johanna Forneck, M.Sc.

Michèle Wessa, Ph.D.

Objective: Neuropsychological deficits and emotion dysregulation are present in symptomatic and euthymic patients with bipolar disorder. However, there is little evidence on how cognitive functioning is influenced by emotion, what the neural correlates of emotional distraction effects are, and whether such deficits are a consequence or a precursor of the disorder. The authors used functional MRI (fMRI) to investigate these questions.

Method: fMRI was used first to localize the neural network specific to a certain cognitive task (mental arithmetic) and then to test the effect of emotional distractors on this network. Euthymic patients with bipolar I disorder (N=22), two populations at high risk for developing the disorder (unaffected first-degree relatives of individuals with bipolar disorder [N=17]), and healthy participants with hypomanic personality traits [N=22]) were tested, along with three age-, gender-, and education-matched healthy comparison groups (N=22, N=17, N=24, respectively).

Results: There were no differences in performance or activation in the task network for mental arithmetic. However, while all participants exhibited slower responses when emotional distractors were present, this response slowing was greatly enlarged in bipolar patients. Similarly, task-related activation was generally increased under emotional distraction; however, bipolar patients exhibited a further increase in right parietal activation that correlated positively with the response slowing effect.

Conclusions: The results suggest that emotional dysregulation leads to exacerbated neuropsychological deficits in bipolar patients, as evidenced by behavioral slowing and task-related hyperactivation. The lack of such a deficit in high-risk populations suggests that it occurs only after disease onset, rather than representing a vulnerability marker.

(Am J Psychiatry 2013; 170:1487–1496)

Bipolar disorder is a chronic, highly debilitating disease. Only 24% of bipolar patients achieve functional recovery 1 year after a manic episode (1), a rate that rises to only 43% after 2 years (2). The level of psychosocial functioning in bipolar patients is correlated with a number of neuropsychological deficits in executive function, attention, and memory (3, 4). These cognitive deficits are present in manic and depressive episodes and even persist into remission (5, 6). It has been hypothesized that the cognitive deficits in bipolar disorder arise, at least in part, from a general hyperreactivity of limbic brain structures and emotional hyperreactivity that interferes with neocortical activity necessary for successful task performance (7, 8). Indeed, heightened amygdala activation at rest and during nonemotional and emotion-related tasks has been seen in symptomatic (9, 10) and euthymic bipolar patients (11–13).

A few studies have investigated cognitive task performance in the presence of emotional distractors. Two studies using the emotional Stroop task found abnormally increased frontal and limbic activity in bipolar patients during color naming of emotional compared with neutral words (11, 14). However, emotion did not affect color-naming response latencies, both in patients and in comparison subjects, suggesting that task processing was not directly influenced. In a previous study (15), we applied an emotional go/no-go task, which yielded behavioral distraction effects in the emotional compared with the neutral condition, but no behavioral alterations in bipolar disorder, although activation was increased in frontal and limbic regions. Similar activation increases without behavioral effects were found in working memory tasks with sad mood induction (16) and face distractor stimuli (17). Critically, these studies could not clarify whether the observed hyperactivations reflect altered processing of the cognitive tasks (e.g., as a compensatory effect) or simply aberrant emotional processing. Addressing this issue would require independent definition of the relevant task network before studying the influence of emotion on this network.

Furthermore, it is unknown whether the potentially increased emotional distractibility is a consequence of the disorder or whether it represents a vulnerability marker. Clinically, this differentiation is critical for refining

TABLE 1. Demographic and Clinical Characteristics of Patients With Bipolar Disorder, Unaffected Relatives, Healthy Participants With Hypomanic Personality, and Their Respective Comparison Counterparts

	Sample 1				
Characteristic	Bipolar Patients (N=22)		Healthy Comparison Subjects (N=22)		Analysis
	Mean	SD	Mean	SD	p
Age (years)	39.4	11.8	40.5	11.8	0.770
Education (years)	11.3	1.6	11.8	1.5	0.293
Intelligence score[a]	105.4	12.6	107.7	14.5	0.592
Handedness (laterality quotient score)[b]	83.8	13.8	85.7	23.1	0.736
Current symptoms					
Young Mania Rating Scale score	1.0	1.6	0	0	0.008
Hamilton Depression Rating Scale score	0.7	1.2	0.1	0.4	0.029
Beck Depression Inventory score	6.7	6.0	1.2	2.0	<0.001
Course of illness					
Age at onset (years)	25.2	7.7			
Age at first hospitalization (years)	27.3	8.2			
Number of previous hospitalizations	3.2	2.5			
Number of depressive episodes	3.6	2.4			
Number of manic episodes	3.0	1.8			
Time in remission (months)	54.0	69.0			
	N	%	N	%	p
Gender					
Female	14	63.6	12	54.5	0.540
Male	8	36.4	10	45.5	
Ever married	12	55.0	13	59.1	0.761
Currently employed	13	59.1	21	95.5	0.004
Medication use					
None	3	13.6			
Antidepressants	7	31.8			
Benzodiazepines	1	4.5			
Antipsychotics	12	54.5			
Lithium carbonate	8	36.4			
Valproic acid	11	50.0			
Lamotrigine	6	27.3			
Substance use					
Caffeine	14	66.7	17	81.0	0.292
Nicotine	6	28.6	2	9.1	0.101
Alcohol	7	31.8	9	40.9	0.531

[a] Measured with the Mehrfachwahl-Wortschatz-Intelligenztest-B.
[b] Measured with the Edinburgh Handedness Inventory.

etiological models of bipolar disorder and designing either targeted therapy or preventive interventions.

In the present study, we aimed to investigate emotional distractibility in patients with bipolar disorder using a two-step functional MRI (fMRI) procedure. The first experiment allowed for the localization of the neural network relevant to a cognitive task, here mental arithmetic. To elucidate the influence of emotion on this network, the second experiment presented arithmetic tasks on top of emotional and neutral distractor images. Using this procedure, we previously found that in healthy subjects, emotional distraction leads to slower performance and increased activation in the task-related neural network, particularly in the parietal cortex (18). The crucial role of this region in arithmetic processing has been repeatedly demonstrated (19, 20). Our approach to testing whether potential deficits represent a vulnerability marker was to investigate remitted patients with bipolar I disorder and two groups of participants at heightened risk for developing bipolar disorder (i.e., unaffected first-degree relatives of bipolar I patients and healthy participants with hypomanic personality [defined using the Hypomanic Personality Scale (21)]), who have been demonstrated to have an increased risk of developing bipolar disorder over time (22). We compared each of these experimental groups with separate matched comparison groups and additionally compared the experimental groups directly with demographic variables as covariates.

If cognitive processing deficits in bipolar disorder are associated with increased emotional distractibility, we would expect an exacerbated behavioral slowing effect and a more pronounced task-related activation increase,

Sample 2					Sample 3				
Relatives (N=17)		Healthy Comparison Subjects (N=17)		Analysis	Hypomanic Personality Participants (N=22)		Healthy Comparison Subjects (N=24)		Analysis
Mean	SD	Mean	SD	p	Mean	SD	Mean	SD	p
36.6	16.2	35.9	15.6	0.898	21.0	1.6	22.3	2.9	0.064
12.5	1.2	12.9	0.3	0.175	13	0	13	0	
103.1	11.8	109.4	12.8	0.157	97.7	5.2	102.3	12.8	0.127
57.7	64.8	80.1	41.1	0.238	82.7	16.9	84.6	16.5	0.715
0	0	0	0		0	0	0	0	
0.3	1.0	0.1	0.5	0.543	0.1	0.5	0.1	0.5	0.904
3.0	3.3	1.8	3.1	0.289	3.5	4.2	1.5	2.7	0.068
N	%	N	%	p	N	%	N	%	p
8	47.1	8	47.1	1.00	13	59.1	14	58.3	0.958
9	52.9	9	52.9		9	40.9	10	41.7	
11	64.7	6	35.3	0.169	0	0	0	0	
15	88.2	15	88.2	1.00	19	86.4	24	100	0.101
10	62.5	13	81.3	0.433	14	63.6	12	52.2	0.550
2	12.5	1	5.9	0.601	9	40.9	3	12.5	0.031
6	35.3	7	41.2	1.00	20	90.9	10	42.7	<0.001

particularly in the parietal cortex, which should also be present in the high-risk groups if these deficits represent a vulnerability marker of bipolar disorder.

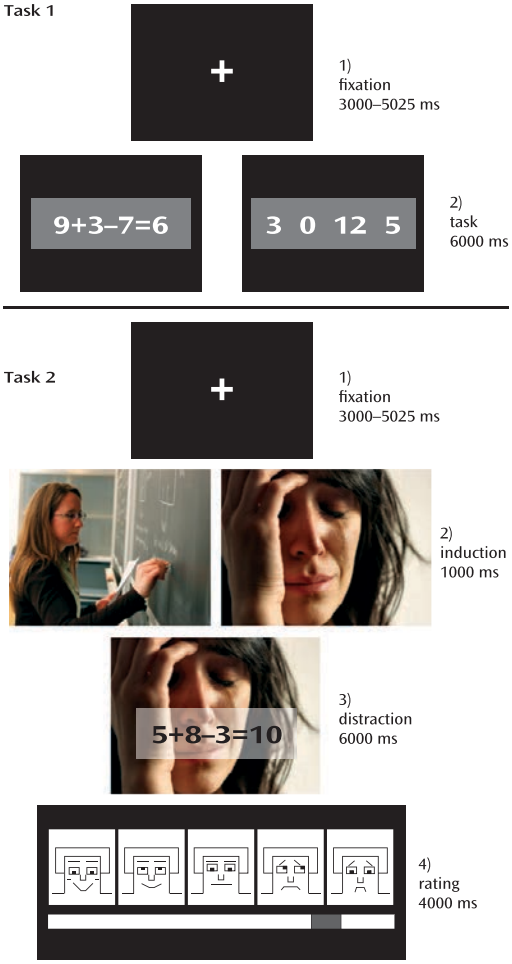
Method

Participants

All participants underwent the Structured Clinical Interview for DSM-IV (23–26), as well as screening for exclusion criteria (neurological disorders, head trauma with loss of consciousness, metal implants, tattoos, substance abuse or dependence, and age <18 or >65). Interviews and observer rating scales for mania (Young Mania Rating Scale [27]) and depression (Hamilton Depression Rating Scale [HAM-D] [28]) were conducted by clinical psychologists, and participants completed the Beck Depression Inventory (BDI [29, 30]). The study was approved by the research ethics committee of the Heidelberg University Faculty of Medicine in Mannheim, Germany. All participants provided written informed consent before entering the study.

Sample 1: bipolar patients and healthy comparison subjects. Twenty-two euthymic bipolar patients and 22 gender-, age-, and education-matched healthy comparison subjects with no history of or current mental disorders participated in the study. Patients were recruited at the Central Institute of Mental Health, Mannheim, Germany, and through local psychiatrists, psychotherapists, and patient support groups. None of the patients currently met criteria for any DSM-IV disorder other than bipolar I disorder. A life chart assessing variables related to illness course was completed for all patients (Table 1). Euthymia was defined as a HAM-D score <5 and a Young Mania Rating Scale score <7 (31). We asked patients about their current medication and verified its stability during the past 6 months. To analyze the psychotropic medication effect, we calculated the total medication load according to a published algorithm (32) reflecting dosage and a variety of different medications (33). The composite measure was generated by summing all individual medication codes for each medication category (mean=2.32, SD=2.08). We then checked for correlations of this index with the effects of interest in bipolar patients.

FIGURE 1. Sequence of Events in the Trial of a Localizer to Identify Brain Activation Patterns Specific to Mental Arithmetic Operations (Task 1) and the Experimental Task To Test the Effects of Emotional Distraction in Mental Arithmetic (Task 2)[a]



[a] The images shown are examples that resemble those in the experiment but are not part of the International Affective Picture System, which was used in this study.

Sample 2: relatives of bipolar patients and healthy comparison subjects. Seventeen unaffected relatives of bipolar I patients and 17 gender-, age-, and education-matched healthy volunteers participated (Table 1). None fulfilled criteria for any lifetime or current mental disorders, and none were taking any psychotropic medications. The relatives were not related to the bipolar patients tested in this study. Five relatives were siblings, four were children, and eight were parents of bipolar patients. Twelve relatives were from simplex families (one case in the family), and five were from multiplex families (at least two cases in the family).

Sample 3: individuals with hypomanic personality and healthy comparison subjects. In previous studies (22, 34), individuals with hypomanic personality were selected based on the Hypomanic Personality Scale, on which scoring in the upper 10% was defined as hypomanic personality (resulting in scores ≥31). Through online questionnaires and in lectures, 1,567 individuals were screened. Twenty-four individuals with hypomanic personality were included, as well as 24 gender-, age-, and education-matched healthy comparison subjects who did not score 0.5 standard deviations above the mean of the distribution (Table 1). For analyses, two participants with hypomanic personality were excluded because of fMRI motion artifacts. None of the participants in this sample fulfilled criteria for mental disorders or reported a positive family history of affective or psychotic disorders, nor were they taking any psychotropic medications. In general, participants with hypomanic personality reported increased caffeine and alcohol consumption; however, none of the study participants consumed alcohol or caffeine beginning the evening of the day before scanning.

Experimental Paradigm

The details of the experimental paradigm have been described elsewhere (18). Briefly, two experimental tasks were presented (Figure 1). Task 1 was a localizer to identify brain activation patterns specific to mental arithmetic operations. In this task, 20 arithmetic problems and 20 number rows were presented for 6,000 ms each, and participants decided whether the presented solution for the equation was correct or whether a "0" was part of the number row.

Task 2 aimed to test the influence of emotional distraction on task processing and presented arithmetic problems equivalent to but different from the problems presented in the localizer task (35). The arithmetic problems were superimposed on 32 highly arousing emotional images (16 negative, 16 positive) and 16 low-arousal neutral images (taken from the International Affective Picture System [36]). Each trial started with 1) a fixation cross presented with a jitter of 3,000–5,025 ms, followed by 2) an emotion induction phase (1,000 ms), 3) the distraction (i.e., the presentation of an arithmetic problem through a transparent overlay on the images; 6,000 ms), and 4) a rating phase (4,000 ms), which was not relevant to this study. Task 2 included 48 mental arithmetic trials. Participants received six training trials before the experiment to familiarize themselves with the procedure.

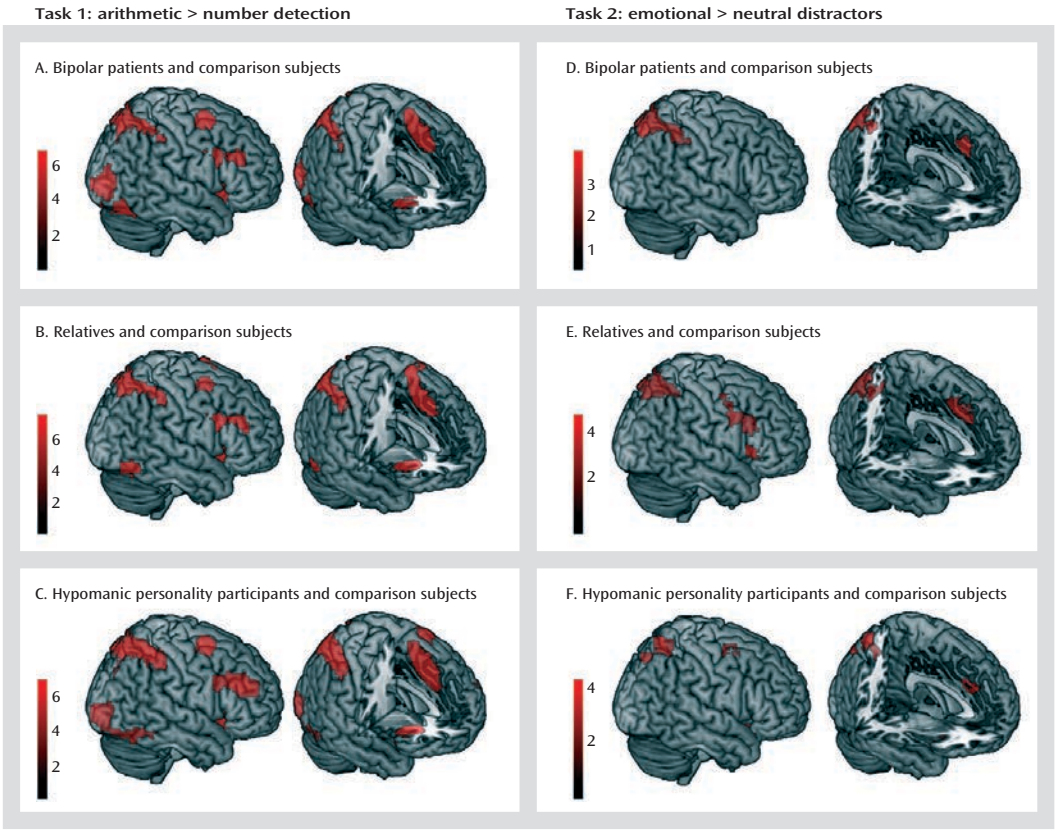
MRI Data Acquisition

MRI data were collected on a Magnetom Tim Trio 3-T scanner (Siemens Medical Solutions, Erlangen, Germany) at the Central Institute of Mental Health, Mannheim. A high-resolution T_1-weighted three-dimensional image was acquired (slice thickness, 1.1 mm, field of view=256×240×176 mm^3, matrix=256×240×160). Functional images were obtained from 40 gradient-echo T_2*-weighted slices (slice thickness, 2.3 mm) per volume. We used a single-shot echo planar sequence with parallel imaging GRAPPA (generalized autocalibrating partially parallel acquisitions) technique (with an acceleration factor of 2)(TR=2,700 ms, flip angle=90°, TE=27 ms, field of view=220 mm^2, matrix=96×96, slice gap=0.7 mm).

fMRI Data Analysis

Image processing and statistical analyses were performed with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Functional images were realigned, slice-time corrected, and spatially normalized using the Montreal Neurological Institute template. For normalization, images were resampled every 3 mm using sinc interpolation. Images were smoothed using a 9×9×9-mm Gaussian kernel.

FIGURE 2. Activation Maps for Mental Arithmetic vs. Number Detection and for Mental Arithmetic on Emotional vs. Neutral Distractor Images



Individual data were analyzed using a general linear model for blood-oxygen-level-dependent (BOLD) signal changes due to the experimental conditions. Movement parameters calculated during realignment were included as parameters of no interest to control for movement artifacts. Individual statistical parametric maps were calculated for the contrasts of interest in order to investigate BOLD signal changes in response to 1) mental arithmetic (task 1: arithmetic problems versus number detection) and 2) the influence of emotion on mental arithmetic (task 2: arithmetic problems superimposed on emotional versus neutral images).

Second-level random-effects analyses were conducted. First, one-sample t tests were calculated for the above-mentioned individual contrast images across participants in each of the three samples. Second, to evaluate differences between the bipolar patients, the at-risk populations, and their respective comparison counterparts, two-sample t tests were computed for all the contrasts. These analyses were not confounded by demographic differences because the groups were carefully matched. Third, to explore differences between the experimental groups directly, we drew a sample from all available healthy comparison subjects that was matched in size to the bipolar group (N=22) and matched in demographic variables as closely as possible to all three experimental groups. We then conducted analyses of variance (ANOVAs) with group as a between-subjects factor (the bipolar, relatives, hypomanic personality, and comparison groups) and age and gender as covariates, since the included groups differed significantly in demographic variables (see Table S1 in the data supplement that accompanies the online edition of this article). Results of these analyses are reported in the data supplement.

For all analyses, because direct contrasts of these conditions yielded no differences in the mental arithmetic task networks, we averaged across negative and positive stimuli and thus enhanced statistical power (18, 35). Activations were thresholded at a whole-brain family-wise-error-corrected p value <0.05, with an extent threshold of 10 voxels in order to protect against false positive activations. From the activations found in task 1, a mask image was created. This mask was then used for task 2, in which activation was also thresholded with a family-wise-error-corrected p value <0.05 and a minimum of 10 voxels.

Behavioral Data Analysis

Reaction times and accuracy were analyzed with SPSS, version 20.0 (IBM, Armonk, N.Y.). Repeated-measures ANOVAs were calculated with group (bipolar patients compared with healthy

TABLE 2. Activations During Task 2 for Mental Arithmetic on Emotional vs. Neutral Distractor Images in Patients With Bipolar Disorder, Unaffected Relatives, Healthy Participants With Hypomanic Personality, and Their Respective Comparison Counterparts and the Activation Difference Between Bipolar Patients and Comparison Subjects

Contrast and Region	Hemisphere	Brodmann's Area	MNI Coordinates (x, y, z)[a]	Cluster Size[b]	Z	T
Bipolar patients plus healthy comparison subjects: emotional > neutral distractors						
Dorsolateral prefrontal cortex	Left	6	–27, –1, 49	160	3.39	3.65
Dorsomedial prefrontal cortex	Right	32	9, 23, 40	155	3.13	3.34
Superior/inferior parietal cortex	Left	7	–15, –76, 52	576	3.63	3.96
	Right	7	18, –79, 49	398	3.54	3.83
Relatives plus healthy comparison subjects: emotional > neutral distractors						
Dorsolateral prefrontal cortex	Right	48	39, 14, 28	206	3.83	4.33
	Right	45	48, 23, 4	58	3.83	4.33
Dorsomedial prefrontal cortex	Right	32	3, 35, 31	281	3.34	3.68
Insula	Left	48	–27, 10, –11	74	3.56	3.96
	Right	48	33, 14, 7	87	3.54	3.94
Superior/inferior parietal cortex	Left	7	–9, –70, 58	476	3.66	4.10
	Right	7	12, –61, 61	339	4.01	4.60
Hypomanic personality participants plus healthy comparison subjects: emotional > neutral distractors						
Dorsolateral prefrontal cortex	Right	6	21, 2, 55	50	3.75	4.08
Dorsomedial prefrontal cortex	Left	32	–9, 26, 25	84	3.22	3.44
Insula	Left	48	–30, 17, –14	41	4.20	4.68
	Right	48	30, 20, –17	19	3.77	4.11
Superior/inferior parietal cortex	Left	5	–18, –58, 61	269	4.05	4.48
	Right	7	21, –61, 64	191	3.92	4.30
Bipolar patients > healthy comparison subjects: emotional > neutral distractors						
Superior/inferior parietal cortex	Right	7	30, –64, 64	61	4.01	4.46

[a] MNI=Montreal Neurological Institute.
[b] Number of activated voxels.

comparison subjects, relatives compared with healthy comparison subjects, and hypomanic personality participants compared with healthy comparison subjects) as a between-subject factor and task (arithmetic, number detection), in Task 1, or emotion (emotional or neutral distractor), in Task 2, as a within-subject factor. As for the imaging data, additional analyses comparing all groups directly were carried out and included age and gender as covariates (see the online data supplement).

Results

Behavioral Data

Task 1. Accuracy was higher in the number detection task than in the arithmetic task (see Table S3 in the online data supplement), which was evident in a main effect of task condition in each sample (sample 1: F=86.7, df=1, 42, $p<0.001$; sample 2: F=60.8, df=1, 32, $p<0.001$; sample 3: F=67.4, df=1, 42, $p<0.001$). There were no significant effects of group or interactions of group and task condition.

Regarding reaction times, there were significant main effects of task condition in each sample (sample 1: F=267.4.5, df=1, 41, $p<0.001$; sample 2: F=168.2, df=1, 32, $p<0.001$; sample 3: F=256.4, df=1, 42, $p<0.001$), with prolonged reactions in the arithmetic task compared with the number detection task, but no group effects were found.

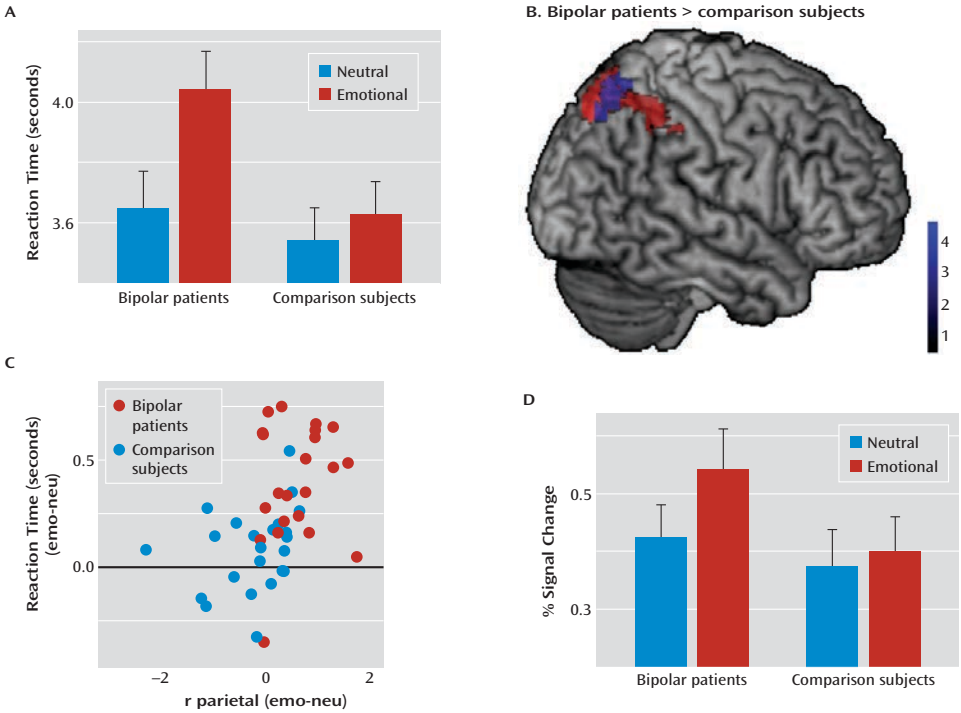
Task 2. For accuracy rates, we observed no significant main effects for distractor condition (emotional compared with neutral images) or group, nor a significant interaction effect (see Table S3 in the data supplement). However, participants were slower in solving arithmetic problems presented on emotional compared with neutral images, as evident in significant main effects of distractor condition on reaction times (sample 1: F=45.0, df=1, 42, $p<0.001$; sample 2: F=6.7, df=1, 32, $p<0.05$; sample 3: F=20.7, df=1, 42, $p<0.001$). We observed no significant main effect of group in any of the samples. While there were no interactions of group with the distractor condition in samples 2 and 3, there was an interaction in sample 1 with bipolar patients and healthy comparison subjects (F=18.7, df=1, 42, $p<0.01$). The difference between bipolar patients and their healthy counterparts was also larger than the difference between the other two groups and their respective comparison counterparts (Δ sample 1 compared with Δ sample 2: t=4.9, df=76, $p<0.001$; Δ sample 1 compared with Δ sample 3: t=6.4, df=88, $p<0.001$).

None of the behavioral effects correlated with medication load.

fMRI Data

Task 1. To elucidate the neural correlates of mental arithmetic, we contrasted the arithmetic task with the number detection task. There were no significant group differences in any of the samples. Therefore, we averaged across the groups in each sample (Figure 2A–C; also see Table S4 in the data supplement), which yielded largely consistent activation patterns. Activation foci included the left and right dorsolateral and dorsomedial prefrontal

FIGURE 3. Reaction Time and Activation Increase in Emotional vs. Neutral Trials[a]



[a] In panel A, reaction times in task 2 for bipolar patients indicate enlarged distraction effects through emotional background images. In panel B, activation differences between bipolar patients and healthy comparison subjects (blue) are shown on the main effect of distraction (red [as displayed in Figure 2D]). Panel C shows the correlation of the reaction time distraction effect and the parietal hyperactivation for mental arithmetic on emotional background images. Panel D shows the respective percent signal change for bipolar patients and comparison subjects.

cortex, the insula, and the parietal cortex, extending into the occipital and ventral temporal cortex. Because the groups did not differ, one mask image for each sample with these networks was created for the analysis for task 2. There were no regions with enhanced activation in the number detection task.

Task 2. To test the influence of emotional distractors on task processing, we contrasted the arithmetic task trials presented on emotional images with those presented on neutral images using the network identified in task 1 as a mask. For emotional background images, we found increased activation in the dorsolateral and dorsomedial prefrontal cortex and the parietal cortex in all three samples and in the left and right insula in samples 2 and 3 (Table 2, Figure 2D–F). There were no differences between relatives or individuals with hypomanic personality and their respective comparison counterparts. However, bipolar patients exhibited increased activation in the right parietal cortex compared with healthy comparison subjects (Figure 3).

The difference in the extracted percent signal change in this region between bipolar patients and healthy comparison subjects was also larger than that between the other two groups and their respective comparison counterparts (Δ sample 1 compared with Δ sample 2: $t=5.4$, $df=76$, $p<0.001$; Δ sample 1 compared with Δ sample 3: $t=4.5$, $df=88$, $p<0.001$).

To relate the right parietal activation increase to the behavioral distraction effect, we correlated the reaction time increase with the activation increase (i.e., the differences between emotional and neutral trials). We found a significant correlation ($r=0.45$, $p<0.01$) (Figure 3), which remained significant when calculating across all participants ($r=0.32$, $p<0.005$).

There were no regions with enhanced activation in response to neutral compared with emotional background images. For the bipolar patients, we also correlated the observed distraction effect with different clinical variables (i.e., the medication load, time in remission, age at illness onset, number of illness episodes, age at first hospitalization, and number of previous hospitalizations), but no significant correlations were observed. Additionally, there were no significant correlations with scores on the BDI,

HAM-D, and Young Mania Rating Scale, with intelligence, or with years of education (see Table S8 in the data supplement).

Discussion

The principal finding of this study is that euthymic bipolar patients experience exacerbated cognitive deficits under emotional distraction; this deficit is specific to bipolar patients in contrast to unaffected high-risk individuals. Bipolar patients exhibited increased response slowing during the arithmetic task while under emotional distraction, which was accompanied by a greater activation increase in a part of the task-related neural network, the right parietal cortex. That relatives of bipolar patients and participants with hypomanic personality were indistinguishable from their respective comparison counterparts suggests that this deficit is a consequence of the disorder rather than a vulnerability marker.

Neither bipolar patients nor high-risk individuals exhibited alterations in behavior or brain activity during the nonemotional mental arithmetic task. The identified neural network underlying mental arithmetic closely conforms with previous reports of clusters in the left and right parietal cortex (19), the dorsolateral and dorsomedial prefrontal cortex (20, 37), and the insula, a common finding in studies of arithmetic processing (18, 38). The lack of group differences in behavioral and neural measures of task performance suggests that there are no general mathematical deficits in remitted bipolar patients and high-risk individuals. This allowed us to use the resulting activation patterns for the definition of one arithmetic task-specific neural network across groups.

When testing for the influence of emotional distractors on this network, bipolar patients exhibited prolonged response slowing. Consistent with our previous data from healthy individuals (18), all participants needed longer to perform the task while under emotional compared with neutral distraction, but this effect was largely increased in the bipolar disorder group. The lack of any effect on error rates demonstrates that participants were still able to solve the equations and compensate for the distraction effect. The fMRI data mirrored this pattern. Task-related activation, particularly in the left and right parietal cortex, but also in the dorsolateral and dorsomedial prefrontal cortex, was increased in all participants under emotional distraction. Thus, it seems to be the additional recruitment of task-specific neural resources that enables individuals to compensate for emotional distraction effects, as has been previously suggested (18, 39–41). Critically, bipolar patients exhibited a larger interference effect than healthy comparison subjects, indicated by further enhanced activation increase in the right parietal cortex. Together with the increased response slowing, this suggests that bipolar patients are more affected by emotional distraction and need to recruit more task-specific neural resources to overcome the distraction effects. That is, those with the greatest distraction-related slowing exhibit the greatest degree of compensation to maintain accuracy in the face of slow performance. These results corroborate previous reports of increased activation in bipolar patients under emotional distraction in the absence of behavioral deficits (11, 14–16). The two-step fMRI procedure applied in our study, however, allows a clear interpretation of the activation increase as task specific, which is further supported by the correlation of increased response times with parietal hyperactivation.

Neither of the studied high-risk populations exhibited the increased emotional distraction effect observed in bipolar patients, although in previous studies, abnormal emotional processing (e.g., in responding to emotional faces) and emotion regulation have been observed in unaffected relatives (42–44) and in individuals with hypomanic personality (45–47). This selective impairment in remitted chronic bipolar patients suggests that increased emotional distractibility is a consequence of bipolar disorder that develops after the experience of at least one illness episode. Emotional stimuli are particularly salient distractors but seem to have an increased potential to impair cognition in bipolar disorder, for which an emotional hyperreactivity is well described. The persistent neuropsychological deficits after bipolar disorder onset are evidence of vulnerable cognitive processing. Our results suggest that this vulnerable system cannot manage emotional distraction as well as before illness onset. Interestingly, there was no correlation with current symptoms or clinical characteristics, such as the number of previous episodes, which may suggest that the deficit occurs after the first illness episode and remains stable thereafter. Future studies should investigate whether emotional distractibility is increased during acute episodes, whether it shows some valence specificity, and whether it increases with the number of experienced episodes. These studies should also compare first-onset and chronic bipolar patients.

Clinically, our findings are highly relevant with regard to patients' functional recovery. Because emotional distraction leads to neuropsychological dysfunction, which in turn predicts functional recovery (3, 4), interventions could include training of selective attention and emotion regulation, since this may be able to enhance sociofunctional integration in euthymic bipolar patients. Establishing such an intervention for improving neuropsychological performance in bipolar patients seems particularly important because these patients may attach emotional meaning even to nonemotional stimuli and tasks (48–50).

There are several limitations to this study. A large proportion of the tested patients continued to receive psychotropic medication. While it has been noted that this may increase generalizability (33), it may also confound the results. We tested for an influence of medication by correlating the effects with a composite medication load

score, which has previously been suggested and successfully applied (33, 51–53). However, future studies should include samples large enough to allow contrasting of drug subgroups and testing for effects in nonmedicated patients. It may also be possible that our sample sizes were not large enough to detect small differences; this is particularly relevant for the comparison of relatives and participants with hypomanic personality with their respective comparison counterparts. However, here the analysis was not only based on null effects in this comparison, but also on observed differences when comparing bipolar patients with any of the other groups (see the online data supplement). Because approximately one-half of the relatives were >30 years old, one might argue that they do not represent a group at high risk but rather possess some resilience factor. However, we found no differences when directly comparing younger and older relatives (see the data supplement), which corroborates the conclusion that the deficit develops only after the experience of an illness episode.

Conclusions

In summary, our results indicate increased emotional distractibility as a consequence of bipolar disorder. Hyperactivation in task-relevant neural regions is related to these behavioral deficits. The findings support a role of disturbed emotion-cognition interactions during the course of bipolar disorder that could critically hinder functional recovery and thus should be a specific target of treatment.

Received Aug. 7, 2012; revisions received March 20 and May 8, 2013; accepted May 17, 2013 (doi: 10.1176/appi.ajp.2013.12081044). From the Section for Experimental Psychopathology and Neuroimaging, Department of General Psychiatry, Center for Psychosocial Medicine, Heidelberg University, Heidelberg, Germany; Department of Social Neuroscience, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany; Department of Clinical Psychology and Neuropsychology, Johannes Gutenberg University, Mainz, Germany; and Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany. Address correspondence to Dr. Kanske (philipp@kanske.de).

The authors report no financial relationships with commercial interests.

Funded by a grant from the Deutsche Forschungsgemeinschaft (grant We3638/3-1).

The authors thank Heike Schmidt for assistance with data acquisition.

References

1. Keck PE Jr, McElroy SL, Strakowski SM, West SA, Sax KW, Hawkins JM, Bourne ML, Haggard P: 12-Month outcome of patients with bipolar disorder following hospitalization for a manic or mixed episode. Am J Psychiatry 1998; 155:646–652
2. Tohen M, Zarate CA Jr, Hennen J, Khalsa HM, Strakowski SM, Gebre-Medhin P, Salvatore P, Baldessarini RJ: The McLean-Harvard First-Episode Mania Study: prediction of recovery and first recurrence. Am J Psychiatry 2003; 160:2099–2107
3. Martínez-Arán A, Vieta E, Colom F, Torrent C, Sánchez-Moreno J, Reinares M, Benabarre A, Goikolea JM, Brugué E, Daban C, Salamero M: Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. Bipolar Disord 2004; 6:224–232
4. Martínez-Arán A, Vieta E, Reinares M, Colom F, Torrent C, Sánchez-Moreno J, Benabarre A, Goikolea JM, Comes M, Salamero M: Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. Am J Psychiatry 2004; 161: 262–270
5. Dittmann S, Fast K, Dederra K, Seemüller F, Möller H-J, Riedel M, Severus E: Kognitive Funktionsfähigkeit bei bipolaren Erkrankungen. Nervenheilkunde 2008; 3:155–164
6. Arts B, Jabben N, Krabbendam L, van Os J: Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives. Psychol Med 2008; 38:771–785
7. Henin A, Micco JA, Wozniak J, Briesch JM, Narayan AJ, Hirshfeld-Becker DR: Neurocognitive functioning in bipolar disorder. Clin Psychol Sci Pract 2009; 16:231–250
8. Strakowski SM, Delbello MP, Adler CM: The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. Mol Psychiatry 2005; 10:105–116
9. Altshuler L, Bookheimer S, Proenza MA, Townsend J, Sabb F, Firestine A, Bartzokis G, Mintz J, Mazziotta J, Cohen MS: Increased amygdala activation during mania: a functional magnetic resonance imaging study. Am J Psychiatry 2005; 162: 1211–1213
10. Almeida JR, Versace A, Hassel S, Kupfer DJ, Phillips ML: Elevated amygdala activity to sad facial expressions: a state marker of bipolar but not unipolar depression. Biol Psychiatry 2010; 67: 414–421
11. Lagopoulos J, Malhi GS: A functional magnetic resonance imaging study of emotional Stroop in euthymic bipolar disorder. Neuroreport 2007; 18:1583–1587
12. Wessa M, Linke J: Emotional processing in bipolar disorder: behavioural and neuroimaging findings. Int Rev Psychiatry 2009; 21:357–367
13. Phillips ML, Ladouceur CD, Drevets WC: A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. Mol Psychiatry 2008; 13:833–857
14. Malhi GS, Lagopoulos J, Sachdev PS, Ivanovski B, Shnier R: An emotional Stroop functional MRI study of euthymic bipolar disorder. Bipolar Disord 2005; 7(suppl 5):58–69
15. Wessa M, Houenou J, Paillère-Martinot ML, Berthoz S, Artiges E, Leboyer M, Martinot JL: Fronto-striatal overactivation in euthymic bipolar patients during an emotional go/nogo task. Am J Psychiatry 2007; 164:638–646
16. Deckersbach T, Rauch SL, Buhlmann U, Ostacher MJ, Beucke JC, Nierenberg AA, Sachs G, Dougherty DD: An fMRI investigation of working memory and sadness in females with bipolar disorder: a brief report. Bipolar Disord 2008; 10:928–942
17. Bertocci MA, Bebko GM, Mullin BC, Langenecker SA, Ladouceur CD, Almeida JR, Phillips ML: Abnormal anterior cingulate cortical activity during emotional n-back task performance distinguishes bipolar from unipolar depressed females. Psychol Med 2012; 42:1417–1428
18. Wessa M, Heissler J, Schönfelder S, Kanske P: Goal-directed behavior under emotional distraction is preserved by enhanced task-specific activation. Soc Cogn Affect Neurosci 2013; 8: 305–312
19. Menon V, Rivera SM, White CD, Glover GH, Reiss AL: Dissociating prefrontal and parietal cortex activation during arithmetic processing. Neuroimage 2000; 12:357–365
20. Ischebeck A, Zamarian L, Schocke M, Delazer M: Flexible transfer of knowledge in mental arithmetic: an fMRI study. Neuroimage 2009; 44:1103–1112

21. Eckblad M, Chapman LJ: Development and validation of a scale for hypomanic personality. J Abnorm Psychol 1986; 95:214–222
22. Kwapil TR, Miller MB, Zinser MC, Chapman LJ, Chapman J, Eckblad M: A longitudinal study of high scorers on the Hypomanic Personality Scale. J Abnorm Psychol 2000; 109:222–226
23. First MB, Gibbon M, Spitzer RL, Williams JBW: Structured Clinical Interview for DSM IV Axis I Disorders (SCID-I). Washington, DC, American Psychiatric Publishing, 1997
24. First MB, Gibbon M, Spitzer RL, Williams JBW, Benjamin L: Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II). Washington DC, American Psychiatric Publishing, 1997
25. Wittchen H-U, Zaudig M, Fydrich T: SKID-I: Strukturiertes Klinisches Interview für DSM-IV. Göttingen, Hogrefe, 1997. [Structural Clinical Interview for DSM-IV Axis I Disorders]
26. Wittchen H-U, Zaudig M, Fydrich T: SKID-II: Strukturiertes Klinisches Interview für DSM-IV. Göttingen, Hogrefe, 1997. [Structural Clinical Interview for DSM-IV Axis II Disorders]
27. Young RC, Biggs JT, Ziegler VE, Meyer DA: A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978; 133:429–435
28. Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56–62
29. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J: An inventory for measuring depression. Arch Gen Psychiatry 1961; 4: 561–571
30. Hautzinger M, Keller F, Kühner C: BDI-II: Beck-Depressions-Inventar Revision. Frankfurt, Pearson Assessment, 2009
31. Mercer L, Becerra R: A unique emotional processing profile of euthymic bipolar disorder? A critical review. J Affect Disord 2013; 146:295–309
32. Sackeim HA: The definition and meaning of treatment-resistant depression. J Clin Psychiatry 2001; 62(suppl 16):10–17
33. Phillips ML, Travis MJ, Fagiolini A, Kupfer DJ: Medication effects in neuroimaging studies of bipolar disorder. Am J Psychiatry 2008; 165:313–320
34. Meyer TD, Drüke B, Hautzinger M: Hypomane persönlichkeit: psychometrische evaluation und erste ergebnisse zur validität der deutschen version der Chapman-Skala. Z Klin Psychol Psychother 2000; 29:35–42
35. Kanske P, Heissler J, Schönfelder S, Bongers A, Wessa M: How to regulate emotion? Neural networks for reappraisal and distraction. Cereb Cortex 2011; 21:1379–1388
36. Lang PJ, Bradley MM, Cuthbert BN: International Affective Picture System (IAPS): Affective Ratings of Pictures and Instruction Manual (Technical Report A–6). Gainesville, University of Florida, Center for Research in Psychophysiology, 2005
37. Rickard TC, Romero SG, Basso G, Wharton C, Flitman S, Grafman J: The calculating brain: an fMRI study. Neuropsychologia 2000; 38:325–335
38. Grabner RH, Ansari D, Koschutnig K, Reishofer G, Ebner F, Neuper C: To retrieve or to calculate? Left angular gyrus mediates the retrieval of arithmetic facts during problem solving. Neuropsychologia 2009; 47:604–608
39. Blair KS, Smith BW, Mitchell DG, Morton J, Vythilingam M, Pessoa L, Fridberg D, Zametkin A, Sturman D, Nelson EE, Drevets WC, Pine DS, Martin A, Blair RJ: Modulation of emotion by cognition and cognition by emotion. Neuroimage 2007; 35:430–440
40. Hart SJ, Green SR, Casp M, Belger A: Emotional priming effects during Stroop task performance. Neuroimage 2010; 49: 2662–2670
41. Pereira MG, de Oliveira L, Erthal FS, Joffily M, Mocaiber IF, Volchan E, Pessoa L: Emotion affects action: midcingulate cortex as a pivotal node of interaction between negative emotion and motor signals. Cogn Affect Behav Neurosci 2010; 10: 94–106
42. Surguladze SA, Marshall N, Schulze K, Hall MH, Walshe M, Bramon E, Phillips ML, Murray RM, McDonald C: Exaggerated neural response to emotional faces in patients with bipolar disorder and their first-degree relatives. Neuroimage 2010; 53: 58–64
43. Olsavsky AK, Brotman MA, Rutenberg JG, Muhrer EJ, Deveney CM, Fromm SJ, Towbin K, Pine DS, Leibenluft E: Amygdala hyperactivation during face emotion processing in unaffected youth at risk for bipolar disorder. J Am Acad Child Adolesc Psychiatry 2012; 51:294–303
44. Green MJ, Lino BJ, Hwang EJ, Sparks A, James C, Mitchell PB: Cognitive regulation of emotion in bipolar I disorder and unaffected biological relatives. Acta Psychiatr Scand 2011; 124: 307–316
45. Carver CS, Johnson SL: Tendencies toward mania and tendencies toward depression have distinct motivational, affective, and cognitive correlates. Cognit Ther Res 2009; 33:552–569
46. Gruber J, Johnson SL, Oveis C, Keltner D: Risk for mania and positive emotional responding: too much of a good thing? Emotion 2008; 8:23–33
47. Kwapil TR, Barrantes-Vidal N, Armistead MS, Hope GA, Brown LH, Silvia PJ, Myin-Germeys I: The expression of bipolar spectrum psychopathology in daily life. J Affect Disord 2011; 130: 166–170
48. Rich BA, Vinton DT, Roberson-Nay R, Hommer RE, Berghorst LH, McClure EB, Fromm SJ, Pine DS, Leibenluft E: Limbic hyperactivation during processing of neutral facial expressions in children with bipolar disorder. Proc Natl Acad Sci USA 2006; 103:8900–8905
49. Strakowski SM, Adler CM, Holland SK, Mills N, DelBello MP: A preliminary fMRI study of sustained attention in euthymic, unmedicated bipolar disorder. Neuropsychopharmacology 2004; 29:1734–1740
50. Adler CM, Holland SK, Schmithorst V, Tuchfarber MJ, Strakowski SM: Changes in neuronal activation in patients with bipolar disorder during performance of a working memory task. Bipolar Disord 2004; 6:540–549
51. Kanske P, Heissler J, Schönfelder S, Wessa M: Neural correlates of emotion regulation deficits in remitted depression: the influence of regulation strategy, habitual regulation use, and emotional valence. Neuroimage 2012; 61:686–693
52. Versace A, Almeida JR, Hassel S, Walsh ND, Novelli M, Klein CR, Kupfer DJ, Phillips ML: Elevated left and reduced right orbitomedial prefrontal fractional anisotropy in adults with bipolar disorder revealed by tract-based spatial statistics. Arch Gen Psychiatry 2008; 65:1041–1052
53. Linke J, King AV, Rietschel M, Strohmaier J, Hennerici M, Gass A, Meyer-Lindenberg A, Wessa M: Increased medial orbitofrontal and amygdala activation: evidence for a systems-level endophenotype of bipolar I disorder. Am J Psychiatry 2012; 169: 316–325

Table S1: Demographic and clinical characteristics of patients with bipolar disorder (bipolar patients, BD), unaffected relatives (relatives, Rel), healthy participants with hypomanic personality (hypomanic personality, Hyp) and 22 selected control participants (Controls, Con).

	Bipolar patients N = 22		**Relatives** N = 17		**Hypomanic personality** N = 22		**Controls** N = 22			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p-value	significant contrasts
Age	39.4	11.8	36.6	16.2	21.0	1.6	32.4	13.2	p < .001**	BD, Rel, Con > Hyp
Years of Education	11.3	1.6	12.5	1.2	13	0	12.6	1.1	p < .001**	Rel, Hyp, Con > BD
Intelligence score	105.4	12.6	103.1	11.8	97.7	5.2	104.2	10.0	p = .119	
Handedness: LQ-Scores	83.8	13.8	57.7	64.8	82.7	16.9	82.4	35.3	p = .090	
Current symptoms										
YMRS	1.0	1.6	0	0	0	0	0	0	p < .001**	BD > Rel, Hyp, Con
HAMD	.7	1.2	0.3	1.0	.1	.5	0	0	p = .016*	BD > Con
BDI	6.7	6.0	3.0	3.3	3.5	4.2	1.5	2.3	p < .001**	BD > Rel, Hyp, Con
	N	%	N	%	N	%	N	%		
Gender Ratio										
Female	14	63.6	8	47.1	13	59.1	13	59.1	p = .587	
Male	8	36.4	9	52.9	9	40.9	9	40.9		
Married lifetime	12	55.0	11	64.7	0	0	7	31.8	p < .001**	BD, Rel, Con > Hyp
Currently employed	13	59.1	15	88.2	19	86.4	21	95.5	p < .05*	Rel, Hyp > BD
Substances										
Caffeine	14	66.7	10	62.5	14	63.6	14	63.6	p = .990	
Nicotine	6	28.6	2	12.5	9	40.9	1	4.5	p < .05*	Hyp > Con
Alcohol	7	31.8	6	35.3	20	90.9	11	50.0	p < .001**	BD, Rel, Con > Hyp

* p < .05
** p < .01

Supplementary Analysis S2

Behavioral data

Task 1

Accuracy was higher in the number detection condition compared to the arithmetical task (supplement Table S3), which was evident in a main effect of task condition across all groups ($F(1,77)=12.4$, $p<.001$). Regarding reaction times, there were significant main effects of task condition across all groups ($F(1,77)=53.3$, $p<.001$), with prolonged reactions in the arithmetic compared to the number detection task. We found no group effects or interactions with group (all $p>.10$).

Task 2

Comparing the three experimental groups and healthy controls, a significant main effect of distractor condition on reaction times ($F(1,77)=40.6$, $p<.001$) was observed, indicating that participants were slower in solving arithmetical problems presented on emotional compared to neutral background images (supplement Table S3).

Additionally, there was an interaction effect of group and distractor condition ($F(1,77)=7.4$, $p<.01$) which indicated an increased effect of emotional distractors in bipolar patients compared to healthy controls and to the other experimental groups (Relatives, Hypomanic personality; all $p<.05$), while there were no further differences between these groups (all $p>.20$).

fMRI analyses

Task 1

The three experimental groups and healthy controls were not significantly different from one another with respect to the contrast of arithmetical task with the number detection task. Therefore, for further

analyses of Task 2, we averaged across all groups to yield one mask image with task-specific activations (supplement Table S5).

Task 2

The analysis across all groups corroborated the results of separate analyses comparing each of the experimental groups (bipolar patients, relatives, hypomanic personality) to a matched healthy control group, showing a significant cluster in a right parietal region for the group by condition interaction (supplement Table S5 and Figure S6). Analysis of the extracted % signal change also yielded a significant interaction of emotional distractor condition and group ($F(3,77) = 3.5$, $p < .05$) as well as a condition main effect ($F(1,77)=4.3$, $p<.05$). Interaction contrasts showed that the effect of emotional distractors was larger in bipolar patients compared to all other groups (all $p<.05$), while there were no further differences between these groups (all $p>.35$).

Table S3: Reaction times and accuracy in Task 1 and Task 2 for bipolar patients, unaffected relatives of bipolar patients, individuals with hypomanic personality, and their respective controls, as well as the 22 selected control participants.

	Task 1			Task 2		
		% correct	Reaction time		% correct	Reaction time
Bipolar	detection	94.6 (11.2)	1.38 (0.36)	neutral	80.1 (16.8)	3.6 (0.6)
patients	arithmetic	73.9 (15.8)	3.89 (1.04)	emotional	80.7 (14.2)	4.0 (0.6)
Controls	detection	96.4 (4.9)	1.25 (0.31)	neutral	90.2 (10.0)	3.5 (0.5)
	arithmetic	77.7 (13.7)	3.86 (0.48)	emotional	88.2 (8.6)	3.6 (0.5)
Relatives	detection	97.6 (3.1)	1.38 (0.46)	neutral	85.7 (12.5)	3.5 (0.6)
	arithmetic	78.2 (12.4)	3.89 (0.47)	emotional	85.8 (11.0)	3.6 (0.5)
Controls	detection	95.3 (15.7)	1.03 (1.48)	neutral	89.0 (9.3)	3.5 (0.5)
	arithmetic	77.9 (14.0)	3.77 (0.47)	emotional	89.0 (7.1)	3.6 (0.5)
Hypomanic	detection	99.1 (2.0)	1.10 (0.19)	neutral	89.2 (13.2)	3.2 (0.5)
Personality	arithmetic	80.5 (13.3)	3.35 (1.21)	emotional	87.8 (11.2)	3.4 (0.6)
Controls	detection	98.3 (3.5)	0.87 (0.97)	neutral	91.8 (8.6)	3.4 (0.4)
	arithmetic	76.0 (19.2)	3.63 (0.44)	emotional	90.8 (5.9)	3.5 (0.4)
Controls	detection	98.5 (2.7)	1.18 (0.28)	neutral	90.8 (8.4)	3.5 (0.4)
	arithmetic	83.1 (6.2)	3.62 (0.39)	emotional	89.6 (5.5)	3.6 (0.4)

Table S4: Activations in Task 1 for mental arithmetic vs. number detection for bipolar patients, unaffected relatives of bipolar patients, individuals with hypomanic personality, and their respective controls.

	H	BA	MNI coordinates			Cs	CI	Z
			x	y	z			
Bipolar patients + Controls: arithmetic > number detection								
dorsolateral prefrontal	L	44	-42	5	28		a	7.44
	R	6	30	-1	52		a	6.57
dorsomedial prefrontal	L	6	-6	11	52	2423	**a**	>8.21
	R	32	9	23	34		a	6.14
Insula	L	48	-33	20	-2		a	7.48
	R	48	33	23	-2	316	**c**	7.48
superior/inferior parietal	L	7	-24	-64	40	4710	**d**	>8.21
	R	7	21	-70	49		d	7.40
occipital/ventral temporal	L	19	-45	-70	-8		d	7.18
	R	19	-42	-82	4		d	6.56
Relatives + Controls: arithmetic > number detection								
dorsolateral prefrontal	L	6	-27	-1	52		a	5.47
	R	6	30	2	55	182	**b**	6.78
dorsomedial prefrontal	L	32	-3	11	49		c	5.85
	R	32	6	17	46	503	**c**	7.38
Insula	L	48	-33	20	1	1242	**a**	7.19
	R	48	36	23	1	629	**d**	>8.21
superior/inferior parietal	L	7	-24	-61	43	3467	**e**	7.58
	R	40	35	-46	43		e	7.10
occipital/ventral temporal	L	19	-45	-76	-2		e	5.73
	R	19	30	-76	7	179	**f**	5.67
Hypomanic personality + Controls: arithmetic > number detection								
dorsolateral prefrontal	L	6	-48	2	45		a	5.89
	R	6	30	2	61	239	**b**	7.49
dorsomedial prefrontal	R	32	6	17	49	2483	**c**	>8.21
insula	L	48	-30	20	-2		c	>8.21
	R	48	36	23	-5	650	**d**	>8.21
superior/inferior parietal	L	7	-24	-70	41	5122	**a**	>8.21
	R	40	39	-43	43		a	>8.21
occipital/ventral temporal	L	19	-42	-79	4		a	5.85
	R	19	27	-79	7		a	5.05

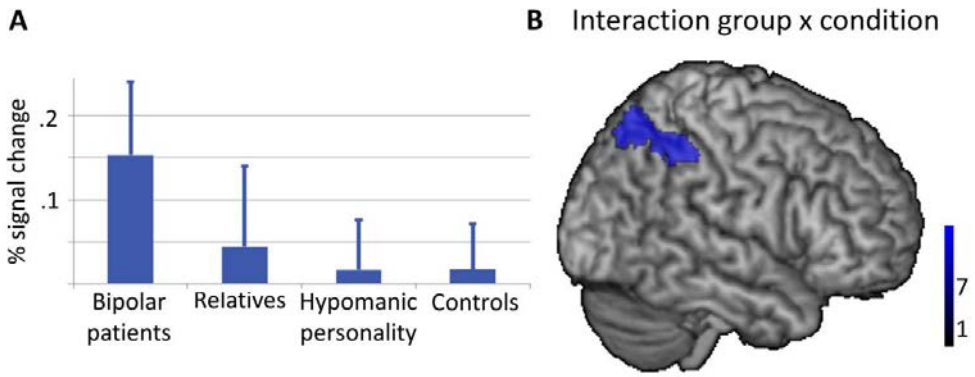
H = Hemisphere; BA = Brodmann area; CS = Cluster size in number of activated voxels; CI = cluster index (all peaks of an activation cluster are identified by the same letter; the cluster peaks are displayed in bold letters)

Table S5: Activations in Task 1 for mental arithmetic vs. number detection and Task 2 for mental arithmetic on emotional vs. neutral distractor images for bipolar patients, unaffected relatives of bipolar patients, individuals with hypomanic personality, and the 22 selected control participants.

	H	BA	MNI coordinates			Cs	CI	Z
			x	y	z			
arithmetic > number detection								
dorsolateral prefrontal	L	44	-42	5	28		a	>8.21
	R	44	45	5	31		a	7.49
dorsomedial prefrontal	L	32	-3	11	52		a	>8.21
	R	32	6	17	49		a	>8.21
insula	L	48	-33	20	-2		a	>8.21
						1638		
	R	48	36	20	-2	6	**a**	>8.21
superior/inferior parietal	L	7	-24	-64	40		a	>8.21
	R	7	27	-61	46		a	>8.21
occipital/ventral temporal	L	19	-47	-70	-11		a	>8.21
	R	19	48	-70	-14		a	6.51
emotional > neutral distractors								
dorsolateral prefrontal	R	46	39	38	31	43	a	5.07
	L	45	-42	29	28	58	b	5.19
dorsomedial prefrontal	R	32	3	17	49	435	c	7.61
insula	L	48	-30	23	1	203	d	6.79
	R	48	33	20	4	219	e	6.89
superior/inferior parietal	L	7	-24	-64	43	4953	f	7.77
	R	7	27	-61	49		f	7.35
Interaction group x condition								
superior/inferior parietal	R	7	27	-58	49	324	a	5.83

H = Hemisphere; BA = Brodmann area; CS = Cluster size in number of activated voxels; CI = cluster index (all peaks of an activation cluster are identified by the same letter; the cluster peaks are displayed in bold letters)

Figure S6: Activations in the right parietal cortex for the interaction of group and distractor condition (A) as well as the respective difference in % signal change for mental arithmetic on emotional vs. neutral background images for all groups (B).



Data supplement for Kanske et al. (doi: 10.1176/appi.ajp.2013.12081044)

Supplementary Analysis S7

To probe the influence of age on the effect in the unaffected first-degree relatives of bipolar patients, we conducted a series of analyses. We first split the group of relatives in those above and below 30 years of age. This yielded two relatively equally sized groups of N = 9 (< 30) and N = 8 (> 30). We then directly contrasted the two age groups, which did not yield any significant differences (even when lowering the threshold to an uncorrected $p < .001$).

We then compared each of the two age groups to their respective healthy control participants. If the effect reflects a resilience characteristic, it should only be observed in the comparison of the older relatives to their controls, not in the younger group that is still at risk. This was, however, not the case. As the power of this small sample is limited, we also compared the size of the effect to that in bipolar patients. The effect size of these comparisons (young relatives $\eta^2=.070$; old relatives $\eta^2=.050$) calculated on the extracted % signal change was less than half the size of that found in bipolar patients and their controls ($\eta^2=.157$).

We also correlated the parietal activation increase for emotional over neutral background images with age in the group of relatives, but observed no significant correlation ($p > .20$). Furthermore, we included age as a covariate in the analysis of Sample 2, which did not yield different results.

Data supplement for Kanske et al. (doi: 10.1176/appi.ajp.2013.12081044)

Table S8: Correlation of the reaction time and right parietal activation distraction effect with clinical and other characteristics in bipolar patients.

	Reaction time (emo - neu)		r parietal activation (emo - neu)	
	r	p	r	p
medication load	.047	.835	-.002	.994
time in remission	.291	.189	.057	.802
age at disease onset	.346	.115	-.327	.138
# of illness episodes	.104	.646	.089	.692
age at first hospitalization	.319	.170	-.299	.201
# of previous hospitalizations	-.241	.293	.191	.406
BDI	-.011	.962	.110	.624
HAMD	-.249	.276	-.249	.277
YMRS	.183	.428	-.156	.500
intelligence	-.124	.591	.083	.720
years of education	-.322	.144	-.111	.623

5.3 Electroencephalographic correlates of biased information processing

This section describes a study establishing a paradigm to implicitly assess biased information processing. Healthy participants were tested and the effects were associated with inter-individual variations in depression related traits.

- Schick, A., Wessa, M., Vollmayr, B., Kuehner, C., **Kanske, P.** (2013). Indirect assessment of an interpretation bias in humans: Neurophysiological and behavioral correlates. *Frontiers in Human Neuroscience, 7*, 272.

frontiers in
HUMAN NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 12 June 2013
doi: 10.3389/fnhum.2013.00272

Indirect assessment of an interpretation bias in humans: neurophysiological and behavioral correlates

Anita Schick[1], Michèle Wessa[1,2]*, Barbara Vollmayr[3], Christine Kuehner[3] and Philipp Kanske[1,4]

[1] Department of General Psychiatry, Section for Experimental Psychopathology and Neuroimaging, Center for Psychosocial Medicine, Heidelberg University, Heidelberg, Germany
[2] Department of Clinical Psychology and Neuropsychology, Institute for Psychology, Johannes Gutenberg-University Mainz, Mainz, Germany
[3] Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim/Heidelberg University, Mannheim, Germany
[4] Department of Social Neuroscience, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

Edited by:
Hadas Okon-Singer, University of Haifa, Israel

Reviewed by:
Limor Lichtenstein-Vidne, Ben Gurion University of the Negev, Israel
Marina Palazova, International Psychoanalytic University Berlin, Germany

***Correspondence:**
Michèle Wessa, Department of Clinical Psychology and Neuropsychology, Institute for Psychology, Johannes Gutenberg-University Mainz, Wallstr. 3, D 55122 Mainz, Germany
e-mail: wessa@uni-mainz.de

Affective state can influence cognition leading to biased information processing, interpretation, attention, and memory. Such bias has been reported to be essential for the onset and maintenance of different psychopathologies, particularly affective disorders. However, empirical evidence has been very heterogeneous and little is known about the neurophysiological mechanisms underlying cognitive bias and its time-course. We therefore investigated the interpretation of ambiguous stimuli as indicators of biased information processing with an ambiguous cue-conditioning paradigm. In an acquisition phase, participants learned to discriminate two tones of different frequency, which acquired emotional and motivational value due to subsequent feedback (monetary gain or avoidance of monetary loss). In the test phase, three additional tones of intermediate frequencies were presented, whose interpretation as positive (approach of reward) or negative (avoidance of punishment), indicated by a button press, was used as an indicator of the bias. Twenty healthy volunteers participated in this paradigm while a 64-channel electroencephalogram was recorded. Participants also completed questionnaires assessing individual differences in depression and rumination. Overall, we found a small positive bias, which correlated negatively with reflective pondering, a type of rumination. As expected, reaction times were increased for intermediate tones. ERP amplitudes between 300 and 700 ms post-stimulus differed depending on the interpretation of the intermediate tones. A negative compared to a positive interpretation led to an amplitude increase over frontal electrodes. Our study provides evidence that in humans, as in animal research, the ambiguous cue-conditioning paradigm is a valid procedure for indirectly assessing ambiguous cue interpretation and a potential interpretation bias, which is sensitive to individual differences in affect-related traits.

Keywords: ERP, N200, LPP, cognitive bias, rumination, reflective pondering

INTRODUCTION

Affective states, including depression, can strongly affect cognitive processes, such as attention, memory, appraisal, and decision-making (Mathews and Macleod, 1994; Beck, 2008; Gotlib and Joormann, 2010; Disner et al., 2011). It has been proposed that a negatively biased interpretation of ambiguous situations results from facilitated attentional processes through emotions (affective priming theories; Bower, 1981; Isen and Daubman, 1984; Isen et al., 1987). This theoretical consideration originates from the semantic network theory, which assumes that associated memories are more easily accessible through a process of "spreading activation" (Anderson and Bower, 1973). In that respect, cognitive theories of depression posit that negative schemata, which are dysfunctional mental representations about the self, trigger a mood congruent interpretation of a distinct situation as good or bad, which itself has consequences on the emotional state of an individual (Beck, 1976). An enduring vicious circle of negative interpretation bias and negative emotional states might then lead to the development of psychopathological conditions, such as affective disorders (Mathews and Macleod, 2005). Indeed, some empirical evidence for negative attention, memory, and interpretation bias related to depression has been provided; however, the results are mixed, probably due to specifics in the selection of stimulus material and assessment of the bias. While studies using questionnaires with ambiguous stories were able to detect a negative interpretation bias in depression (Butler and Mathews, 1983; Berna et al., 2011), other studies that used measures like response latency or startle reflex were only in part successful. Lawson and Macleod (1999) studied the naming latency of words in positive or negative valence presented after an affective prime sentence and found no relation to scores in the Beck Depression Inventory (BDI; Beck et al., 1996). In contrast, participants with a higher BDI score showed larger startle reflex amplitudes elicited by ambiguous merge words compared to neutral stimuli (Lawson et al., 2002). This is in line with the hypotheses of a negative interpretation bias in depression as the startle reflex amplitude is

known to be increased after negative stimuli (Bradley et al., 1990; Lang et al., 1990).

Apart from clinical depression, individual coping style has been proposed to influence the interpretation of a situation as positive or negative. Lyubomirsky and Nolen-Hoeksema (1995) have shown that rumination, a coping style that refers to focusing one's attention and thoughts on negative aspects of a situation (Nolen-Hoeksema et al., 2008), leads to more negative interpretations of hypothetical situations. Using more explicit measures of cognitive bias, Kuehner and Huffziger (2012) showed that an induced ruminative self-focus after negative mood induction significantly increased dysfunctional depressiogenic attitudes in healthy individuals.

The heterogeneity of results in clinical as well as analogous samples (e.g., healthy individuals with elevated induced or naturally occurring negative mood), might, at least in part, result from methodological difficulties with experimental tasks that were used to assess biased information processing (see above). In the present study, we therefore adopted an ambiguous cue-conditioning paradigm from animal research that indirectly assesses biased information processing. In an acquisition phase, participants first learn to discriminate two tones of different frequency, which are followed by either a positive or a negative consequence. This part of the paradigm is similar to affective (or evaluative) conditioning which has been shown to be effective in various fields of research (De Houwer et al., 2001). Using a learning procedure similar to affective conditioning and pairing stimuli with reinforcers has repeatedly led to valence transfer as reported in the visual (Stolarova et al., 2006; Schacht et al., 2012) and auditory domain (Laufer and Paz, 2012). In a second phase of the paradigm participants are confronted with additional tones of intermediate frequency that are not reinforced. The response to these ambiguous tones is used as an indicator of an interpretation bias.

This experimental setup has several advantages. First, the auditory cues are indeed neutral in the beginning of the experimental procedure and have no negative or positive connotation. Also, as the intermediate tones are never followed by feedback, they are truly ambiguous which is essential for a cognitive bias to affect decision-making. This is in contrast to a study by Anderson et al. (2012), who applied a similar paradigm to assess emotional biases. In this study, however, the intermediate tones were also reinforced, which renders them non-ambiguous and, therefore, did not allow for the detection of an inherent interpretation bias. Second, this experimental setup was initially developed in rodents (e.g., Harding et al., 2004; Enkel et al., 2010). Its adaptation to human research paves the way for translational research that offers new possibilities for identifying neural and molecular mechanisms underlying biased information processing as well as the potential of developing new treatment strategies. Using such an ambiguous cue-conditioning paradigm, Enkel et al. (2010) successfully distinguished between congenitally non-helpless and helpless rats, which served as an animal model of depression. Moreover, Richter et al. (2012) showed that the negative bias of helpless rats was decreased after enrichment supporting the idea of using such bias as a measurement sensitive to depression treatment.

To also elucidate the neural time-course underlying biased information processing, we assessed event-related brain potentials (ERPs) of the EEG. Promising potentials include the N2 component, peaking around 200 ms post-stimulus over frontocentral electrode sites, which is associated with cognitive control and response conflict (Folstein and Van Petten, 2008). In the present study, ambiguous stimuli make demands on cognitive control processes (e.g., in cancelling a prepared response) and induce response conflict due to perceptual similarity and unclear response demands. N2 amplitude increases have been reported for increasing perceptual similarity (Folstein and Van Petten, 2004) and for increasing difficulty to discriminate ambiguous stimuli (Szmalec et al., 2008).

In addition, a positive deflection of the ERP starting around 300 ms post-stimulus has been consistently related to emotion and arousal (see Olofsson et al., 2008). As discussed by Kissler et al. (2009), this potential has been variously termed P3, late positive potential (LPP), or late positive complex (LPC). For the present study, we will use the term LPP for this positivity. There is evidence showing it to be increased for emotional stimuli (Foti et al., 2009; Hajcak et al., 2010; Kaestner and Polich, 2011) even when controlling for arousal (e.g., Rozenkrants and Polich, 2008; Kaestner and Polich, 2011; Feng et al., 2012) and it is also related to subjective intensity ratings of emotion (Cuthbert et al., 2000). Interestingly, it has also been reported to differentiate between negatively and positively conditioned stimuli (Schacht et al., 2012).

Late positive ERP components with a maximum over frontal electrode sites have also been associated with executive processes involved in categorization (Folstein and Van Petten, 2011) and there is evidence for an interaction between categorization and emotional valence modulating the LPP. In categorization tasks, negative stimuli have been found to elicit larger LPPs than either positive or neutral stimuli (Kanske and Kotz, 2007). Here again, the interpretation of the ambiguous tones may be reflected in the LPP amplitude. Therefore, in the present study, the LPP may be increased for reference tones because of their association with reward and punishment and could also reflect the differential processing of positively and negatively interpreted ambiguous tones.

In sum, the main goal of the present study was to test the described ambiguous cue-conditioning paradigm in humans. Therefore, we aimed at (1) establishing that the intermediate tones are perceived as ambiguous by comparing reference and intermediate tones, and (2) elucidating the processing of negatively and positively interpreted ambiguous stimuli. As pointed out above, interpretation of ambiguous stimuli is influenced by affective states and cognitive styles. We therefore assessed current affect, depression, and rumination. We hypothesized that ambiguity of the intermediate tones would be reflected in uncertain response choices, increased response times, and increased amplitudes of the N2 due to difficult discriminability and unclear response demands resulting in response conflict. We also expected LPP amplitudes to be increased for the non-ambiguous reference tones because of their greater behavioral relevance and associated affective salience. We further hypothesized the specific interpretation of ambiguous stimuli to be reflected in differential

ERP responses, specifically LPP amplitudes, which might show increases for negatively interpreted tones.

MATERIALS AND METHODS

PARTICIPANTS

Participants were recruited via advertisements at the universities of Mannheim and Heidelberg. They received course credits and obtained the monetary gain from the ambiguous cue-conditioning task according to their task performance (see below for details). In total, 20 participants (10 women) with a mean age of 24.2 years ($SD = 9.1$) took part in the experiment. All had normal or corrected to normal vision and normal hearing. One participant reported to be left-handed. Since we had no lateralization hypotheses and as the results did not change, when excluding this participant, we report data with this participant included. None of the participants reported a history of head injuries, tinnitus, or mental disorders. After being informed about the experiment the participants gave written informed consent. The study was approved by the local Ethics Committee of Heidelberg University and was conducted in accordance with the Declaration of Helsinki.

MATERIALS

Stimuli consisted of five sinusoidal tones with a fundamental frequency between 1000 and 1164 Hz. They were selected so that all tones had a distance of 0.25 Bark ($f_1 = 1000$ Hz, $f_2 = 1038$ Hz, $f_3 = 1078$ Hz, $f_4 = 1120$ Hz, $f_5 = 1164$ Hz). The total duration of the tones was 250 ms with a linear ramp of 20 ms. For feedback a yellow smiley or a red frowney were presented (see **Figure 1**).

EXPERIMENTAL PROCEDURE

Participants were tested in an electrically shielded room in a single experimental session. They were seated in front of a monitor screen (1 m distance). To adjust the loudness of the tones to the individual hearing level, participants were presented a sinusoidal tone of 1000 Hz, which decreased in loudness, and pressed a button as long as they heard the tone. This procedure was repeated 10 times. The intensity of the test tones was then scaled according to the individual hearing level (Moore, 2003). The experimental task was to discriminate two reference tones (tone 1 and 5) by pressing one of two buttons with their right index or middle finger, respectively. One of the reference tones is referred to as "positive tone" (PT) as it acquired positive valence over the course of the experiment through positive feedback (smiley) and monetary gain (15 cents) after a correct button press. If participants responded incorrectly to this tone, they were informed that they had "missed the chance to win" money. In this case, a picture of a crossed smiley was shown. The other reference tone is referred to as "negative tone" (NT), as participants lost 15 cents when they pressed the incorrect button and negative feedback (frowney) was presented. By pressing the correct button to the NT, participants could prevent money loss and were presented with a crossed frowney and the information that loss of money had been avoided. If participants did not press any button within a response window of 1 s, they either lost money when the NT was presented or missed the chance to win money when the PT was presented. Each trial was comprised of a tone lasting 250 ms, a response window of 750 ms,

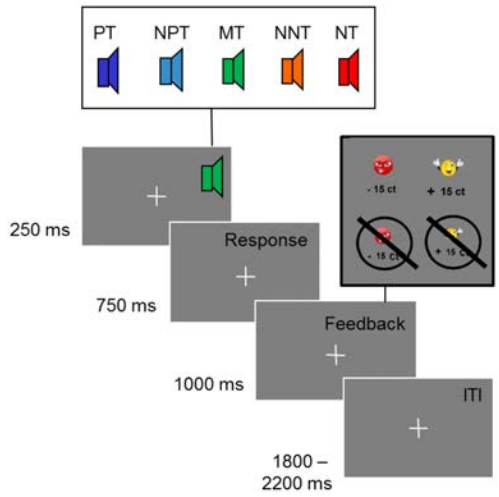


FIGURE 1 | Ambiguous cue-conditioning paradigm. PT, positive tone; NPT, near-positive tone; MT, middle tone; NNT, near-negative tone; NT, negative tone. Participants were instructed to press a button after each tone to obtain reward or avoid loss of reward (0.15 €). After the button press participants received a feedback. In case of a correct identification of the positive tone, they saw a smiley indicating a monetary gain. For a wrong button press or no response, they saw a crossed smiley indicating that they had missed the chance to earn money. A correct identification of the negative tone was followed by a picture of a crossed frowney indicating that they had successfully avoided loosing money; for a wrong button press, participants lost money and saw a frowney. No feedback was presented after intermediate tones (NPT, MT, NNT) and after 4% of the reference tones (PT, NT). The inter-trial-interval (ITI) was jittered between 1800 and 2200 ms.

the following feedback lasting 1 s and, finally, a jittered inter-trial interval of 2 s on average (randomly selected between 1800 and 2200 ms) (see **Figure 1**). Participants were randomly assigned to one of four counterbalanced conditions with respect to the finger used for button presses and the fundamental frequency of PT and NT.

During a brief learning and a training session, participants learned to discriminate PT and NTs. First, both tones were presented five times each and participants were told how to respond (learning session). Second, discrimination of reference tones was practiced with 40 randomized trials (training session). In the experimental test phase, three additional tones were presented (66 times each) in addition to the two reference tones (PT, NT; 282 times each). The three additional tones were intermediate in frequency (see section Materials) and labeled near-positive tone (NPT), middle tone (MT), and near-negative tone (NNT). The three intermediate tones were not followed by any feedback to render them fully ambiguous. All tones were presented in pseudo-randomized order. Furthermore, during the test phase 24 (4%) of the reference tones (12 PT, 12 NT) were also presented without feedback to cover the presence of intermediate tones. Thus, a total of 222 tones were presented without feedback, another 540 trials

(270 PT, 270 NT) were presented with positive or negative feedback. All tones without feedback were less frequent than reference tones with feedback to cover their presence and to keep the participants motivated. Participants were instructed to respond to each tone by pressing one of the two buttons and they were informed that not every trial would have a feedback. The test phase was divided into six blocks of 127 trials, each lasting about 8 min. At the end of each block participants had a break of 2 min in which they were informed about the total amount of money won up to that point.

QUESTIONNAIRES

Several questionnaires were used to explore inter-individual differences in emotional state and trait variables. We measured current depression with the German version of the Beck Depression Inventory II (Beck et al., 1996; Hautzinger et al., 2006), a 21 item self-report questionnaire. To investigate strategies for coping with depressive symptoms participants completed a German version of the Response Style Questionnaire (RSQ; Nolen-Hoeksema, 1991), which tests for two subcomponents of rumination: "reflective pondering" and "brooding" (10 items; Gonzalez et al., 2003; Kuehner and Huffziger, 2012). Furthermore, participants completed the Positive and Negative Affect Scale (20 Items; Watson et al., 1988) immediately before the ambiguous cue-conditioning task.

EEG RECORDING

During the ambiguous cue-conditioning task, a continuous 64 channel EEG was recorded using Ag/AgCl-electrodes positioned according to the international 10/20 system. The signals were amplified by Neuroscan Synamp amplifiers (Compumedics, Charlotte, NC, USA), digitized at a rate of 500 Hz and recorded by Neuroscan Scan 4 Acquire software (Compumedics, Charlotte, NC, USA). The right mastoid was used as on-line reference and an electrode positioned on the sternum was used as ground electrode. Another electrode was placed on the left mastoid (for offline re-referencing). Horizontal eye movements were recorded from two electrodes placed lateral to both eyes, while two electrodes placed above and below the right eye registered vertical eye movements. Impedances of all electrodes were kept below 15 kOhm.

DATA ANALYSIS

For the EEG data analyses, Brain Vision Analyzer software (Brain Products GmbH, Munich) was used. The pre-processing of the EEG data included re-referencing to the mean of the mastoids and down-sampling to 200 Hz. Then, the data were filtered (0.1–30 Hz) to remove high- and low-frequency waves and the data were visually inspected to check for artifacts. To correct for eye movement artifacts, we performed an independent component analysis (Comon, 1994). In a next step, segments of 1200 ms starting 200 ms pre-stimulus and ending 1000 ms after stimulus onset were created. Using the semiautomatic artifact rejection tool, segments were excluded if the minimum and maximum amplitude in a segment differed by more than 300 μV. To obtain event-related potentials (ERPs), the segments were averaged relative to a 200 ms pre-stimulus baseline.

For the statistical analyses of behavioral, questionnaire, and ERP data, SPSS Statistics 18 (SPSS Inc., Chicago, IL, USA) was used. To test for effects of ambiguity we compared behavioral and ERP responses to the reference and to the intermediate tones. Because of the very low number of incorrect responses to the reference tones, only the correct response trials were included for analyses of reaction time and ERP data. To analyze the participants' response choice, a difference score between the frequencies of the two response options (positive, negative) was calculated, reflecting the degree of uncertainty in associating a tone with a response. This difference score was then compared between reference and intermediate tones.

To test for effects of interpretation biases, we analyzed the responses to the three intermediate tones since the participants' response reflects the categorization of the ambiguous tones as either predicting reward or punishment. Here, we calculated 3×2 repeated measures ANOVAs with the factors tone (NNT, MT, NPT) and response (positive, negative). Also, to obtain an overall measure of the cognitive bias, which can be correlated with questionnaire scores, we calculated a bias score defined as the mean of all responses to the three intermediate tones. A response to avoid punishment (negative response) was calculated as -1 while a response to obtain reward (positive response) counted $+1$. A positive bias score indicates more positive than negative responses, while a negative bias score indicates more negative than positive responses to the ambiguous tones. An independent sample t-test was computed to test for gender differences in the bias score. To test if the bias changed during the test phase, a One-Way ANOVA with the factor block (1–6) was calculated.

In this study, ERP analyses focused on N2 and LPP. Based on the literature (Folstein and Van Petten, 2008) we extracted the mean activity in the time window from 180 to 240 ms post-stimulus for analyzing the conflict-related N2 component. For LPP analyses, we first calculated an omnibus ANOVA of the mean activity with the factors tone (NNT, NPT, MT), response (positive, negative), and electrode for consecutive time windows of 100 ms up to 1000 ms. These analyses showed a significant response by electrode interaction in the time window from 300 to 700 ms. For the analyses of the ambiguity effect we chose a shorter time window from 0 to 500 ms for the omnibus ANOVA with the factor ambiguity (reference tones, intermediate tones) and electrode since analyses of the later time windows would be confounded by feedback-related activity that occurred on average 540 ms post-stimulus (as a feedback was only presented after reference tones, not after the intermediate tones). Based on the results obtained here we focused further analyses on the time window from 300 to 500 ms. We then exported mean activity in the time range 300–500 ms (early LPP) and 300–700 ms (late LPP) and performed analyses per electrode. Based on these analyses we defined two regions of interest (frontal: F1, Fz, F2, FC1, FCz, and FC2; posterior: P1, Pz, P2, PO3, POz, and PO4) that we included in further analyses.

To link behavioral data with ERP results and questionnaire data, we computed bivariate Spearman correlations. For all analyses significant thresholds of $p < 0.05$ were used and significant main effects and interactions were followed up

with Bonferroni corrected *post-hoc* paired comparisons or contrasts. A Greenhouse-Geisser correction was applied when necessary.

RESULTS

BEHAVIORAL FINDINGS

Response choice

Participants were well able to discriminate the two reference tones as indicated by 86.9% ($SD = 20$) correct responses in the training session. In the following test phase, the percentage of correct responses to the reference tones was similarly high (mean percentage of correct responses: 87.0%; $SD = 7$), despite the presentation of additional intermediate tones (see **Figure 2A**).

To test for the effects of ambiguity on response choice, we compared responses to the reference and to the intermediate tones. Specifically, we compared the absolute difference between the percentage of positive and negative button presses. For the reference tones, this yielded a mean difference score of 81.73% ($SD = 11.56$). For the intermediate tones the index was 45.68% ($SD = 13.70$), indicating a more undetermined response pattern. A repeated measures ANOVA with the factor ambiguity (reference tones, intermediate tones) was significant [$F_{(1)} = 143.73$; $p < 0.001$; partial $\eta^2 = 0.88$].

To check for effects of interpretation biases, we compared the number of negative and positive responses to the three intermediate tones. A repeated measures ANOVA with tones (NNT, MT, NPT) and responses (negative, positive) yielded a significant effect of tone [$F_{(1.07)} = 12.13$; $p < 0.01$; partial $\eta^2 = 0.39$], which points to differences between NNT and MT ($p < 0.001$), as well as NPT and MT ($p < 0.001$) as indicated by pairwise comparisons. A significant tone by response interaction [$F_{(1)} = 189.72$; $p < 0.001$; partial $\eta^2 = 0.91$] was driven by a higher percentage of positive responses to NPT and a higher percentage of negative responses to NNT [$F_{(1)} = 355.40$; $p < 0.001$; partial $\eta^2 = 0.95$].

Reaction time

Figure 2B displays the reaction time data for all tone and response combinations. To test for the effect of ambiguity on reaction times, we again compared reference and intermediate tones. This effect was significant indicating that participants responded faster to the reference compared to the intermediate tones [$F_{(1)} = 27.64$; $p < 0.001$; partial $\eta^2 = 0.59$].

To test for the effect of interpretation biases, the three intermediate tones were compared with repeated measures ANOVA with the factors tone (NPT, MT, NNT) and response (positive, negative). This analysis showed a significant tone by response interaction [$F_{(2)} = 18.45$; $p < 0.001$; partial $\eta^2 = 0.49$]. *Post-hoc* contrasts showed that this interaction was due to faster responses to obtain reward than to avoid punishment after NPT [$F_{(1)} = 19.44$; $p < 0.001$; partial $\eta^2 = 0.51$] and faster responses to avoid punishment than to obtain reward after NNT [$F_{(1)} = 11.85$; $p < 0.005$; partial $\eta^2 = 0.38$]. Positive and negative responses to MT were equally fast ($p > 0.90$).

Individual differences in bias score

In the current sample the bias score was slightly positive with a mean of 3.95 ($SD = 44.8$) but not significantly different from 0 [$t_{(19)} = 3.94$; $p = 0.70$]. To test if the bias changed throughout the experiment, we calculated a One-Way ANOVA with the factor block, which was not significant indicating constant interpretation of the intermediate tones across the six experimental blocks ($p > 0.5$). We also observed no gender differences ($p > 0.5$). Furthermore, there was no significant correlation of cognitive bias with current mood (PANAS) and depression (BDI; all $p > 0.5$). We did, however, observe a significant correlation between the bias score and the reflective pondering subscale of the RSQ, indicating that participants with a higher score in reflective pondering displayed a more negative bias ($\rho = -0.50$; $p = 0.025$; see **Figure 3**) while the brooding subscale did not correlate with the bias score ($p > 0.5$).

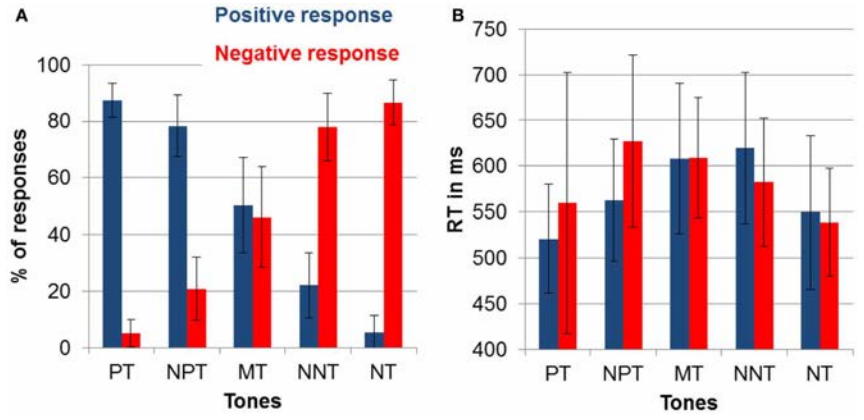


FIGURE 2 | (A) Percentage of chosen responses (and SD) to avoid punishment (negative response) and obtain reward (positive response) for each of the five tones. **(B)** Mean reaction times (and SD) to the five tones.

ERP RESULTS

Across conditions the following ERP components were detected: a negative deflection peaking around 200 ms after tone onset (N2) and a positive deflection starting around 300 ms after tone onset (LPP).

In order to define the latency range of these components we calculated several omnibus ANOVAs per electrode. Besides the effect for electrode in each time window, we obtained a significant effect for ambiguity from 400 to 500 ms [$F_{(60)} = 10.24$; $p < 0.01$; partial $\eta^2 = 0.39$] and significant interactions for ambiguity and electrode [300–400 ms: $F_{(60)} = 1.83$; $p < 0.001$; partial $\eta^2 = 0.1$; 400–500 ms: $F_{(60)} = 2.56$; $p < 0.001$; partial $\eta^2 = 0.14$]. Further analyses focused on the time window from 300 to 500 ms.

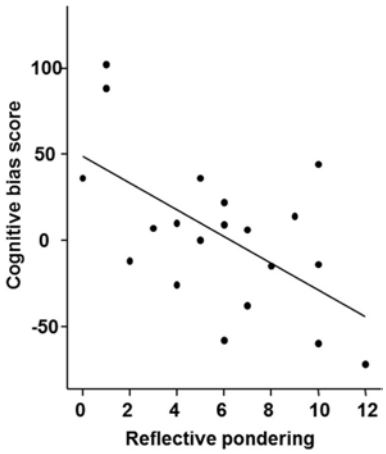


FIGURE 3 | Correlation of the cognitive bias score with the reflective pondering subscale of the Response Style Questionnaire ($p < 0.05$; $\rho = -0.501$).

For the interpretation bias effect omnibus ANOVAs revealed main effects for electrode in each time window and in addition effects for response in the time window from 300 to 400 ms [$F_{(1)} = 4.4$; $p < 0.05$; partial $\eta^2 = 0.22$] and from 600 to 700 ms [$F_{(1)} = 11.76$; $p < 0.01$; partial $\eta^2 = 0.4$]. Further, the analyses showed a significant response by electrode interaction in the time windows from 300 to 400 ms [$F_{(60)} = 2.6$; $p < 0.001$; partial $\eta^2 = 0.14$], from 400 to 500 ms [$F_{(60)} = 2.0$; $p < 0.001$; partial $\eta^2 = 0.11$], from 500 to 600 ms [$F_{(60)} = 1.9$; $p < 0.001$; partial $\eta^2 = 0.11$] and from 600 to 700 ms [$F_{(60)} = 1.68$; $p < 0.001$; partial $\eta^2 = 0.1$]. Thus, analyses focused on the time window from 300 to 700 ms.

Ambiguity effect

To test for the effects of ambiguity, we calculated an ANOVA with the factors ambiguity (reference tones, intermediate tones) and region (anterior, posterior). For the early LPP time window (300–500 ms), we identified significant main effects of ambiguity [$F_{(1)} = 6.0$; $p < 0.05$; partial $\eta^2 = 0.27$] and region [$F_{(1)} = 54.75$; $p < 0.001$; partial $\eta^2 = 0.78$]. As shown in **Figure 4**, early LPP amplitudes were larger for reference compared to ambiguous tones and over posterior compared to anterior electrodes. The interaction of ambiguity and region was not significant ($p > 0.1$). For the N2, only a significant effect of region [$F_{(1)} = 79.45$; $p < 0.001$; partial $\eta^2 = 0.82$] with larger N2 amplitudes over frontal

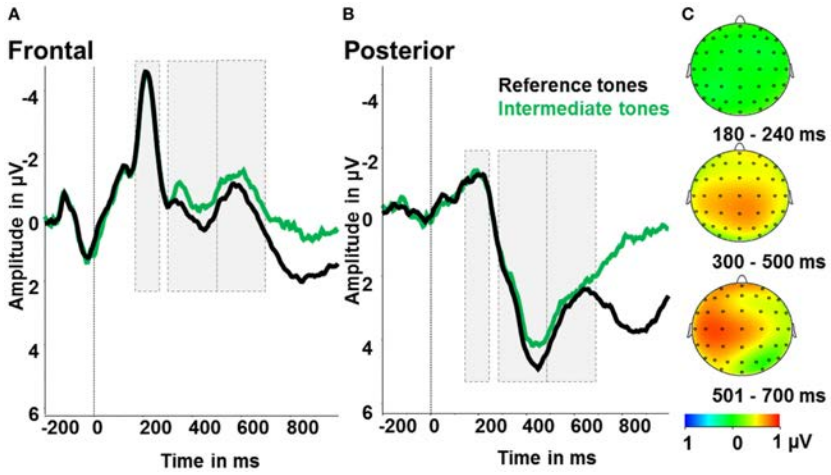


FIGURE 4 | Ambiguity effect: ERPs after reference tones (black) and intermediate tones (green). (A) Event-related activity averaged over frontal electrodes (F1, Fz, F2, FC1, FCz, FC2). **(B)** Event-related activity averaged over posterior electrodes (P1, Pz, P2, PO3, POz, PO4). **(C)** Maps display the activity difference of the reference tones and correct responses minus ambiguous tones and all responses in µV in the time windows 180–240 ms (N2), 300–500 ms (early LPP) and 501–700 ms (late LPP) post-stimulus.

compared to posterior electrodes was found. Further main effects or interactions were not significant (all $p > 0.5$, see **Figure 4**).

Interpretation bias effect

To test for indicators of different processing of positively or negatively interpreted stimuli, we compared intermediate tones with positive and negative responses. Therefore, we conducted repeated measures ANOVAs with the factors tone (NPT, MT, NNT), response (positive, negative), and region (frontal, posterior). For the LPP in the time window 300–700 ms post-stimulus there were significant effects of response [$F_{(1)} = 4.55$; $p < 0.05$; partial $\eta^2 = 0.22$] with larger amplitudes after negative responses and a main effect of region with larger amplitudes over posterior electrode sides [$F_{(1)} = 65.08$; $p < 0.001$; partial $\eta^2 = 0.80$]. Besides, there was a significant response by region interaction [$F_{(1)} = 11.21$; $p < 0.01$; partial $\eta^2 = 0.41$]. Over frontal electrodes, amplitudes were increased after negatively, as opposed to positively, categorized intermediate tones [$F_{(1)} = 11.11$; $p < 0.01$; partial $\eta^2 = 0.41$], while there were no effects over posterior electrode sites (all $p > 0.5$; see **Figure 5**). For the N2, a significant effect of region [$F_{(1)} = 63.29$; $p < 0.001$; partial $\eta^2 = 0.78$] with larger N2 amplitudes over frontal compared to posterior electrodes was found. Further main effects or interactions were not significant in this time range (all $p > 0.5$, see **Figure 5**).

DISCUSSION

The current study employed an ambiguous cue-conditioning paradigm for the indirect assessment of an affect-related interpretation bias and investigated the related neurophysiological correlates with EEG. In contrast to instrumental conditioning procedures, this paradigm comprised a second stage introducing additional stimuli intermediate in frequency to the learned ones. Ambiguity of these intermediate tones could be established with participants responding slower and with less certainty when confronted with the intermediate tones. In the current sample of healthy individuals, a small positive cognitive bias was observed which was associated with inter-individual differences in ruminative coping style, i.e., reflective pondering. Higher scores in reflective pondering were related to a more negative bias. Also, the data yield insight into the time-course of ambiguous stimulus interpretation showing decreases in LPP amplitudes after ambiguous tone presentation, but no N2 effect. Moreover, we observed differences in ERP amplitudes depending on the interpretation of the ambiguous stimuli: frontal LPP amplitudes were increased for negatively compared to positively interpreted intermediate tones.

AMBIGUITY EFFECT

For the validity of the present paradigm it is essential that the intermediate tones are perceived as ambiguous with regard to what potential outcome they predict. Evidence for this is the increased response uncertainty that participants showed by selecting positive and negative responses equally often after the intermediate tones, while the responses to the reference tones were either clearly positive or negative. Additionally, response times were longer for intermediate tones also indicating increased response uncertainty (Szmalec et al., 2008; Anderson et al., 2012).

The collected ERP data can shed light on the time-course of processing ambiguity in the intermediate tones. In contrast to our hypotheses, we observed no effect of ambiguity on the N2. As ambiguity has been conceptualized as representing a form of cognitive conflict (Szmalec et al., 2008), we would have expected to see increased N2 amplitudes for ambiguous vs. reference tones, analogous to incongruent vs. congruent stimuli in conflict tasks like the flanker or Stroop (van Veen and Carter, 2002). A critical

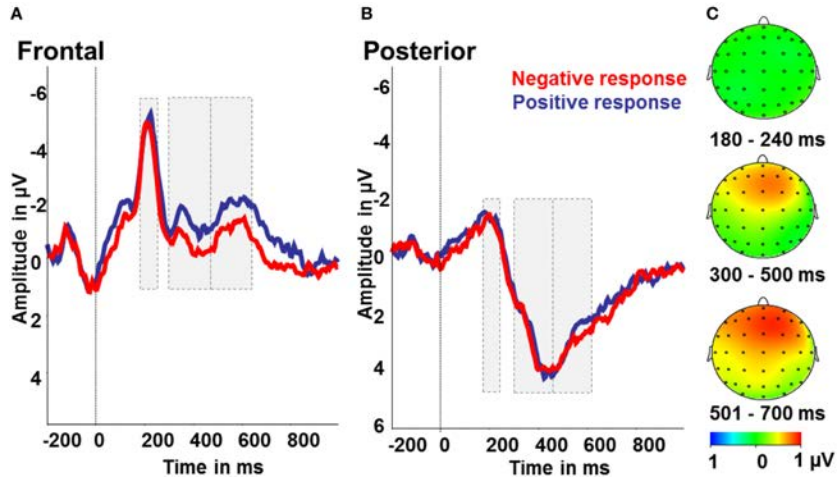


FIGURE 5 | Interpretation bias effect: ERP amplitudes for positive (blue) and negative responses (red) to the intermediate tones. (A) Frontal region of interest. **(B)** Posterior region of interest. **(C)** Activity difference of ambiguous tones and positive responses minus ambiguous tones and negative responses in µV in the time windows 180–240 ms (N2), 300–500 ms (early LPP) and 501–700 ms (late LPP) post-stimulus onset.

difference from previous reports of N2 increases for ambiguous stimuli (Szmalec et al., 2008) is the affective context in the present study. Szmalec et al. (2008) also had participants differentiate two tones of variably perceptual similarity, but responses were not associated with reward or punishment. Positive and negative emotional stimuli, however, have been shown to modulate processing of cognitive conflict and the related N2 amplitude (Kanske and Kotz, 2010, 2011). In particular, the N2 is enlarged for stimuli of greater emotionality, reflecting increased recruitment of cognitive control processes (for an overview see Kanske, 2012). In the present study, it could be argued that the reference tones possess more emotional salience due to their association with potential monetary gain or loss, thus recruiting more cognitive control resources. This may have raised N2 amplitudes to the level of the ambiguous tones. The pattern of LPP amplitude changes corroborates this explanation. We observed increased LPP amplitudes for the reference compared to the intermediate tones, which suggests that the reference tones were perceived as more salient. The LPP has been consistently found to be increased for emotional and arousing stimuli of different modalities (Cuthbert et al., 2000; Schupp et al., 2003; Foti et al., 2009; Schacht and Sommer, 2009; Hajcak et al., 2010). In addition, P3 which peaks in a similar time range has been associated with task relevance (for a review see Kok, 2001). In the present study, task relevance is arguably higher for the reference tones, as they are followed by monetary gains and losses, while the responses to the intermediate tones are without consequences.

In sum, the ERP data suggest that the reference tones in the present task were of higher salience than the intermediate tones, reflected in increased LPP amplitudes, which may have overridden an ambiguity effect in the N2 time window.

Since participants were presented with a visual feedback after the reference tones (which occurred on average 540 ms after stimulus onset), but not after the intermediate tones, the ERP cannot be meaningfully interpreted in the late LPP time window. The late positive deflection which is increased for reference compared to intermediate tones from 540 ms post-stimulus onwards is most likely due to this visual stimulation.

INTERPRETATION BIAS EFFECT

A second question we addressed concerned the differences in processing between positive and negative interpretations of the ambiguous intermediate tones. The absence of a strong overall bias means that about half of the intermediate tones were interpreted negatively and positively. This pattern varied, however, as NPT and NNTs were interpreted more often as positive and negative, respectively. Interpretations in the opposite direction (e.g., a negative response to a NPT) were also slowed down. The major question here was whether the decision to respond to a tone positively or negatively is associated with differential processing of the tones. The effect of tone interpretation on LPP amplitudes suggests that this is the case. The amplitudes were increased for tones that were subsequently responded to with a negative compared to a positive button press. This direction of the effect falls in line with several previous studies that showed enlarged positivities for different types of emotional stimuli (Kanske and Kotz, 2007; Rozenkrants and Polich, 2008; Kaestner and Polich, 2011; Feng et al., 2012). The present data, however, add to this evidence that the top-down interpretation of the affective value of a certain stimulus yields similar brain responses as when the affective value is inherent in the stimulus. Previously, Schacht et al. (2012) found increased LPP amplitudes for stimuli with learned positive valence. The authors suggest that this finding might be due to better learning for the positive compared to negative reinforcers. The present results show an effect on LPP amplitude due to the interpretation and association of the intermediate tones with a certain valence. The fact that we find enlarged LPP amplitudes for negatively interpreted tones might be explained by task differences. In our study, participants received feedback on their response and thus learned a tone—response association leading to one positive and one NT. In contrast, Schacht et al. (2012) used picture sets of different valence (as rated a priori) and participants had to classify the pictures in positive, neutral, or negative without feedback. Beyond that, the focus of our analyses was on intermediate tones that were not reinforced in the acquisition phase. Here, we find processing differences apparent already from around 300 ms post-stimulus in the LPP. Even though the more anterior distribution of this component is not typical, some variability in the topography of valence effects in the P3 time window has been reported (Rozenkrants and Polich, 2008; Feng et al., 2012). Principal components analyses of valence-related ERP effects corroborate this, showing a number of late positivities that might only partially share neural generators because of different scalp distribution (Foti et al., 2009). The exact role of these differentiable components still needs to be specified, however.

INTERPRETATION BIAS AND ITS RELATIONSHIP TO AFFECT-RELATED VARIABLES

We suggested that valence is ascribed to the intermediate tones on the basis of an individual interpretation preference that biases cognitive processing. However, here we observed no significant correlations between current positive or negative mood or depression and interpretation bias, although this has previously been reported (Eysenck et al., 1991; Mogg et al., 2006; Anderson et al., 2012). The lack of a relationship between current mood and depressive symptoms with the interpretation bias in the present study might result from a very limited variance in these affect-related variables in young healthy individuals (e.g., BDI ranging from 0 to 8 on a scale with a maximum score of 63, see **Table 1**). Nevertheless, we did observe a significant negative correlation between the bias score and reflective pondering, a subcomponent of rumination. This might indicate that individuals with a stronger ruminative coping style show a more negative bias and vice versa. Joormann et al. (2006) have also studied the relation between cognitive bias and rumination. Here, an attentional bias toward sad faces correlated significantly with brooding, a second subcomponent of rumination as measured with the RSQ, but not with reflective pondering. From this finding, the authors concluded that there might be functional as well as dysfunctional components of rumination. However, in depressed patients both rumination subscales (brooding and reflective pondering) were increased compared to healthy controls (Joormann et al., 2006). There are several explanations for the finding of a relationship between reflective pondering and a negative interpretation

Table 1 | Questionnaire data.

	Minimum	Maximum	Mean	*SD*
BDI	0	8	2.85	2.46
RSQ_R	0	12	5.80	3.40
RSQ_B	1	8	4.45	2.46
PA	18	39	28.65	6.72
NA	10	18	11.00	1.89

Range, mean, and standard deviation (SD) of participants' scores in the Beck Depression Inventory (BDI), Reflective pondering subscale (RSQ_R), and Brooding subscale (RSQ_B) of the Response Style Questionnaire, and positive (PA) and negative affect (NA) assessed before the measurement with the Positive and Negative Affect Scale (PANAS).

bias, while no such relationship was found between brooding and biased information processing. First, questionnaire data show that the variance for brooding was much smaller than for reflective pondering, limiting the potential to find a correlation. Second, whereas in clinical depression reflective pondering might represent the more adaptive ruminative coping style (in comparison to brooding), it still indicates a ruminative coping style that is maladaptive when compared to more adaptive cognitive coping strategies, such as positive reappraisal, positive refocusing, or focusing on planning. Our result of a negative correlation between reflective pondering and the interpretation bias is in line with previous studies relating cognitive bias and rumination (Gotlib and Joormann, 2010; Koster et al., 2011) and encourages further research with clinical samples using the described paradigm as it suggests that a maladaptive, depressive cognitive style is related to negative interpretation bias.

That, on a group level, we did not observe a significant interpretation bias may be plausible, given the fact that we investigated a group of healthy individuals that rather tend to show a positive bias (Deldin et al., 2001). Further, it is supposed that cognitive biases result from depressiogenic schemata and that they are not active until triggered by a negative event or a negative mood state (Scher et al., 2005). Thus, negative mood or thought induction may be necessary to elicit a negative cognitive bias in control participants. With the induction of self-focused thoughts which are similar to ruminative thinking, Hertel and El-Messidi (2006) observed more negative interpretations of ambiguous homographs in dysphoric students. Future research could combine mood induction procedures with the present paradigm to test for changes in the measured bias.

LIMITATIONS

Although the present study provides a validation of an animal experimental setup that allows the indirect assessment of an interpretation bias and gives new insights into the time-course of ambiguous cue processing, a number of limitations have to be pointed out. First, we did not assess other, more explicit measures of cognitive bias in addition to the ambiguous cue-conditioning task, which could have added some external validity to the present results. Second, we did not collect valence rating for the tones after the conditioning paradigm, which could have corroborated their acquired valence status. In a later yet unpublished study we included valence ratings. In this study participants ascribed more positive valence to the PT than to the NT and the intermediate tones. The NT did not differ in valence which might be due to the fact that only false responses to the NT had negative consequences. A direct loss after the NT would be a stronger negative feedback and more comparable to the punishing effect of an electric shock in the study by Enkel et al. (2010). Apart from the valence transfer to the intermediate tones their categorization might also be influenced by the sensory resemblance of the NPT to the PT and the NNT to the NT. Sensory similarity might facilitate the affective interpretation of these tones or affective interpretation might partly be a consequence of the sensory similarity. If sensory similarity was the only basis for decision-making then the responses would be identical to the ones after the corresponding reference tones. The present results indicate that responses to these tones are biased by both the frequency information of the tones and top-down interpretations. In case of the MT sensory resemblance plays no role since these tones resemble neither the PT nor the NT. Responses to these tones might therefore underlie a cognitive bias more strongly. In addition, the intermediate tones might differ in their degree of ambiguity. Although the lack of feedback after all three intermediate tones leads to uncertainty as seen by an increase in reaction time, the sensory resemblance of NPT and NNT might facilitate response selection. Thus, MT represents the highest level of ambiguity. In the present study the number of MT was too small for statistical analyses but further studies could increase the number by only presenting MT and no NNT or NPT. Another limitation of the paradigm might be that it lacks a neutral condition. Presenting another tone which is either followed by neutral feedback or where the participant does not need to respond would further corroborate the affective conditioning procedure. Finally, as the present study was designed to validate the employed experimental task and to delineate the neurophysiological mechanisms of ambiguous cue processing and biased interpretation of ambiguous cues, we were not able to detect a relation of the interpretation bias with depression measures. As this was probably due to the small variance in depression scores in the present sample, future studies should test clinical samples with the procedure. Although the correlational findings of the present study suggest an association between interpretation bias and rumination, our sample size was very small. Besides, we did not correct for multiple comparisons underlining the rather exploratory nature of our findings although it is under debate if Bonferroni corrections are appropriate (Perneger, 1998). To corroborate our findings mood or rumination inductions (e.g., Huffziger and Kuehner, 2009) would be necessary. But, we also have to point out that the literature on cognitive biases in depression is inconsistent (for reviews see Dalgleish and Watts, 1990; Gotlib and Joormann, 2010). Especially studies using implicit measures of cognitive bias fail to detect a negative interpretation bias (Lawson and Macleod, 1999) even after negative mood induction (Bisson and Sears, 2007).

CONCLUSION

The present study aimed at establishing an ambiguous cue-conditioning paradigm in humans. Such an approach has the

advantage that it assesses the interpretation bias indirectly, which yields it unaffected by demand effects or a priori connotations of the applied stimulus material (as is the case, for example, in words; Lawson and Macleod, 1999; or homophones; Mogg et al., 2006). Furthermore, it offers the possibility of testing for positive and negative biases by assigning affective significance (positive and negative, respectively) to two initially neutral tones through classical conditioning. After such an acquisition phase, the test phase introduced tones of intermediate frequency that served as a measure of interpretation bias since the response to these tones indicated the participants' expectation of a rewarding or potentially punishing event.

The results of the present study provide evidence that ambiguous cue processing and resulting interpretation bias is assessable by using the proposed ambiguous cue-conditioning task that has previously been established in animals. On a behavioral level, ambiguous stimuli led to uncertainty in their response options and longer reaction times. On a neurophysiological level, we observed no N2 differences, but increased LPP amplitudes for reference stimuli compared to ambiguous stimuli, suggesting greater task-relevance and emotional salience for the reward- and punishment-related stimuli. Interpretation of the ambiguous stimuli had an effect on LPP over frontal electrodes with increased amplitudes for a negative compared to a positive interpretation. This indicates early and prolonged differences in the activation of top-down interpretation mechanisms.

ACKNOWLEDGMENTS

This work was funded by the Deutsche Forschungsgemeinschaft (SFB636, Project C6 and D4) and a PhD scholarship to Anita Schick from Heidelberg University.

REFERENCES

Anderson, J. R., and Bower, G. H. (1973). *Human Associative Memory*. Washington, DC: Winston and Sons.

Anderson, M. H., Hardcastle, C., Munafò, M. R., and Robinson, E. S. J. (2012). Evaluation of a novel translational task for assessing emotional biases in different species. *Cogn. Affect. Behav. Neurosci.* 12, 373–381. doi: 10.3758/s13415-011-0076-4

Beck, A. T. (1976). *Cognitive Therapy and the Emotional Disorders*. Oxford, England: International Universities Press.

Beck, A. T. (2008). The evolution of the cognitive model of depression and its neurobiological correlates. *Am. J. Psychiatry* 165, 969–977. doi: 10.1176/appi.ajp.2008.08050721

Beck, A. T., Steer, R. A., and Brown, G. K. (1996). *Manual for the Beck Depression Inventory-II*. San Antonio, TX: Psychological Corporation.

Berna, C., Lang, T. J., Goodwin, G. M., and Holmes, E. A. (2011). Developing a measure of interpretation bias for depressed mood: an ambiguous scenarios test. *Pers. Individ. Dif.* 51, 349–354. doi: 10.1016/j.paid.2011.04.005

Bisson, M. A. S., and Sears, C. R. (2007). The effect of depressed mood on the interpretation of ambiguity, with and without negative mood induction. *Cogn. Emot.* 21, 614–645. doi: 10.1080/02699930600750715

Bower, G. H. (1981). Mood and memory. *Am. Psychol.* 36, 129–148. doi: 10.1037/0003-066X.36.2.129

Bradley, M. M., Cuthbert, B. N., and Lang, P. J. (1990). Startle reflex modulation: emotion or attention? *Psychophysiology* 27, 513–522. doi: 10.1111/j.1469-8986.1990.tb01966.x

Butler, G., and Mathews, A. (1983). Cognitive processes in anxiety. *Adv. Behav. Res. Ther.* 5, 51–62. doi: 10.1016/0146-6402(83)90015-2

Comon, P. (1994). Independent component analysis, A new concept? *Signal Process.* 36, 287–314. doi: 10.1016/0165-1684(94)90029-9

Cuthbert, B. N., Schupp, H. T., Bradley, M. M., Birbaumer, N., and Lang, P. J. (2000). Brain potentials in affective picture processing: covariation with autonomic arousal and affective report. *Biol. Psychol.* 52, 95–111. doi: 10.1016/S0301-0511(99)00044-7

Dalgleish, T., and Watts, F. N. (1990). Biases of attention and memory in disorders of anxiety and depression. *Clin. Psychol. Rev.* 10, 589–604. doi: 10.1016/0272-7358(90)90098-U

De Houwer, J., Thomas, S., and Baeyens, F. (2001). Associative learning of likes and dislikes: a review of 25 years of research on human evaluative conditioning. *Psychol. Bull.* 127, 853–869. doi: 10.1037/0033-2909.127.6.853

Deldin, P. J., Keller, J., Gergen, J. A., and Miller, G. A. (2001). Cognitive bias and emotion in neuropsychological models of depression. *Cogn. Emot.* 15, 787–802. doi: 10.1080/02699930143000248

Disner, S. G., Beevers, C. G., Haigh, E. A. P., and Beck, A. T. (2011). Neural mechanisms of the cognitive model of depression. *Nat. Rev. Neurosci.* 12, 467–477. doi: 10.1038/nrn3027

Enkel, T., Gholizadeh, D., Halbach, O. V. B. U., Sanchis-Segura, C., Hurlemann, R., Spanagel, R., et al. (2010). Ambiguous-cue interpretation is biased under stress- and depression-like states in rats. *Neuropsychopharmacology* 35, 1008–1015. doi: 10.1038/npp.2009.204

Eysenck, M. W., Mogg, K., May, J., Richards, A., and Mathews, A. (1991). Bias in interpretation of ambiguous sentences related to threat in anxiety. *J. Abnorm. Psychol.* 100, 144–150. doi: 10.1037/0021-843X.100.2.144

Feng, C., Wang, L., Liu, C., Zhu, X., Dai, R., Mai, X., et al. (2012). The time course of the influence of valence and arousal on the implicit processing of affective pictures. *PLoS ONE* 7:e29668. doi: 10.1371/journal.pone.0029668

Folstein, J. R., and Van Petten, C. (2004). Multidimensional rule, unidimensional rule, and similarity strategies in categorization: event-related brain potential correlates. *J. Exp. Psychol. Learn. Mem. Cogn.* 30, 1026–1044. doi: 10.1037/0278-7393.30.5.1026

Folstein, J. R., and Van Petten, C. (2008). Influence of cognitive control and mismatch on the N2 component of the ERP: a review. *Psychophysiology* 45, 152–170. doi: 10.1111/j.1469-8986.2007.00602.x

Folstein, J. R., and Van Petten, C. (2011). After the P3: late executive processes in stimulus categorization. *Psychophysiology* 48, 825–841. doi: 10.1111/j.1469-8986.2010.01146.x

Foti, D., Hajcak, G., and Dien, J. (2009). Differentiating neural responses to emotional pictures: evidence from temporal-spatial PCA. *Psychophysiology* 46, 521–530. doi: 10.1111/j.1469-8986.2009.00796.x

Gonzalez, R., Nolen-Hoeksema, S., and Treynor, W. (2003). Rumination reconsidered: a psychometric analysis. *Cogn. Ther. Res.* 27, 247–259. doi: 10.1023/A:1023910315561

Gotlib, I. H., and Joormann, J. (2010). Cognition and depression: current status and future directions. *Annu. Rev. Clin. Psychol.* 6, 285–312. doi: 10.1146/annurev.clinpsy.121208.131305

Hajcak, G., Macnamara, A., and Olvet, D. M. (2010). Event-related potentials, emotion, and emotion regulation: an integrative review. *Dev. Neuropsychol.* 35, 129–155. doi: 10.1080/87565640903526504

Harding, E. J., Paul, E. S., and Mendl, M. (2004). Animal behaviour: cognitive bias and affective state. *Nature* 427, 312. doi: 10.1038/427312a

Hautzinger, M., Keller, F., and Kuehner, C. (2006). *Das Beck Depressionsinventar, I. I. Deutsche Bearbeitung und Handbuch zum BDI II*. Frankfurt am Main: Hartcourt Test Services.

Hertel, P. T., and El-Messidi, L. (2006). Am I blue? Depressed mood and the consequences of self-focus for the interpretation and recall of ambiguous words. *Behav. Ther.* 37, 259–268. doi: 10.1016/j.beth.2006.01.003

Huffziger, S., and Kuehner, C. (2009). Rumination, distraction, and mindful self-focus in depressed patients. *Behav. Res. Ther.* 47, 224–230. doi: 10.1016/j.brat.2008.12.005

Isen, A. M., and Daubman, K. A. (1984). The influence of affect on categorization. *J. Pers. Soc. Psychol.* 47, 1206–1217. doi: 10.1037/0022-3514.47.6.1206

Isen, A. M., Daubman, K. A., and Nowicki, G. P. (1987). Positive affect facilitates creative problem solving. *J. Pers. Soc. Psychol.* 52, 1122–1131. doi: 10.1037/0022-3514.52.6.1122

Joormann, J., Dkane, M., and Gotlib, I. H. (2006). Adaptive and maladaptive components of rumination? diagnostic specificity and relation to depressive biases. *Behav. Ther.* 37, 269–280. doi: 10.1016/j.beth.2006.01.002

Kaestner, E. J., and Polich, J. (2011). Affective recognition memory processing and event-related brain potentials. *Cogn. Affect. Behav. Neurosci.* 11, 186–198. doi: 10.3758/s13415-011-0023-4

Kanske, P., and Kotz, S. A. (2007). Concreteness in emotional words: ERP evidence from a hemifield study. *Brain Res.* 1148, 138–148. doi: 10.1016/j.brainres.2007.02.044

Kanske, P., and Kotz, S. A. (2010). Modulation of early conflict processing: N200 responses to emotional words in a flanker task. *Neuropsychologia* 48, 3661–3664. doi: 10.1016/j.neuropsychologia.2010.07.021

Kanske, P., and Kotz, S. A. (2011). Conflict processing is modulated by positive emotion: ERP data from a flanker task. *Behav. Brain Res.* 219, 382–386. doi: 10.1016/j.bbr.2011.01.043

Kanske, P. (2012). On the influence of emotion on conflict processing. *Front. Integr. Neurosci.* 6:42. doi: 10.3389/fnint.2012.00042

Kissler, J., Herbert, C., and Junghofer, M. (2009). Emotion and attention in visual word processing—an ERP study. *Biol. Psychol.* 80, 75–83. doi: 10.1016/j.biopsycho.2008.03.004

Kok, A. (2001). On the utility of P3 amplitude as a measure of processing capacity. *Psychophysiology* 38, 557–577. doi: 10.1017/S0048577201990559

Koster, E. H. W., De Lissnyder, E., Derakshan, N., and De Raedt, R. (2011). Understanding depressive rumination from a cognitive science perspective: the impaired disengagement hypothesis. *Clin. Psychol. Rev.* 31, 138–145. doi: 10.1016/j.cpr.2010.08.005

Kuehner, C., and Huffziger, S. (2012). Response styles to depressed mood affect the long-term course of psychosocial functioning in depressed patients. *J. Affect. Disord.* 136, 627–633. doi: 10.1016/j.jad.2011.10.019

Lang, P. J., Bradley, M. M., Cuthbert, B. N. (1990). Emotion, attention, and the startle reflex. *Psychol. Rev.* 97, 377–395. doi: 10.1037/0033-295X.97.3.377

Laufer, O., and Paz, R. (2012). Monetary loss alters perceptual thresholds and compromises future decisions via amygdala and prefrontal networks. *J. Neurosci.* 32, 6304–6311. doi: 10.1523/JNEUROSCI.6281-11.2012

Lawson, C., and Macleod, C. (1999). Depression and the interpretation of ambiguity. *Behav. Res. Ther.* 37, 463–474. doi: 10.1016/S0005-7967(98)00131-4

Lawson, C., Macleod, C., and Hammond, G. (2002). Interpretation revealed in the blink of an eye: depressive bias in the resolution of ambiguity. *J. Abnorm. Psychol.* 111, 321–328. doi: 10.1037/0021-843X.111.2.321

Lyubomirsky, S., and Nolen-Hoeksema, S. (1995). Effects of self-focused rumination on negative thinking and interpersonal problem solving. *J. Pers. Soc. Psychol.* 69, 176–190. doi: 10.1037/0022-3514.69.1.176

Mathews, A., and Macleod, C. (1994). Cognitive approaches to emotion and emotional disorders. *Annu. Rev. Psychol.* 45, 25–50. doi: 10.1146/annurev.ps.45.020194.000325

Mathews, A., and Macleod, C. (2005). Cognitive vulnerability to emotional disorders. *Annu. Rev. Clin. Psychol.* 1, 167–195. doi: 10.1146/annurev.clinpsy.1.102803.143916

Mogg, K., Bradbury, K. E., and Bradley, B. P. (2006). Interpretation of ambiguous information in clinical depression. *Behav. Res. Ther.* 44, 1411–1419. doi: 10.1016/j.brat.2005.10.008

Moore, B. C. J. (2003). *An Introduction to the Psychology of Hearing, Fifth Edition.* Amsterdam: Academic Press.

Nolen-Hoeksema, S. (1991). *Response Styles Questionnaire. Unpublished Manuscript.* Stanford, CA: Stanford University.

Nolen-Hoeksema, S., Wisco, B. E., and Lyubomirsky, S. (2008). Rethinking rumination. *Perspect. Psychol. Sci.* 3, 400–424. doi: 10.1111/j.1745-6924.2008.00088.x

Olofsson, J. K., Nordin, S., Sequeira, H., and Polich, J. (2008). Affective picture processing: an integrative review of ERP findings. *Biol. Psychol.* 77, 247–265. doi: 10.1016/j.biopsycho.2007.11.006

Perneger, T. (1998). What's wrong with Bonferroni adjustments. *BMJ* 316, 1236–1238. doi: 10.1136/bmj.316.7139.1236

Richter, S. H., Schick, A., Hoyer, C., Lankisch, K., Gass, P., and Vollmayr, B. (2012). A glass full of optimism: enrichment effects on cognitive bias in a rat model of depression. *Cogn. Affect. Behav. Neurosci.* 12, 527–542. doi: 10.3758/s13415-012-0101-2

Rozenkrants, B., and Polich, J. (2008). Affective ERP processing in a visual oddball task: arousal, valence, and gender. *Clin. Neurophysiol.* 119, 2260–2265. doi: 10.1016/j.clinph.2008.07.213

Schacht, A., Adler, N., Chen, P. Y., Guo, T. M., and Sommer, W. (2012). Association with positive outcome induces early effects in event-related brain potentials. *Biol. Psychol.* 89, 130–136. doi: 10.1016/j.biopsycho.2011.10.001

Schacht, A., and Sommer, W. (2009). Emotions in word and face processing: early and late cortical responses. *Brain Cogn.* 69, 538–550. doi: 10.1016/j.bandc.2008.11.005

Scher, C. D., Ingram, R. E., and Segal, Z. V. (2005). Cognitive reactivity and vulnerability: empirical evaluation of construct activation and cognitive diatheses in unipolar depression. *Clin. Psychol. Rev.* 25, 487–510. doi: 10.1016/j.cpr.2005.01.005

Schupp, H. T., Junghöfer, M., Weike, A., and Hamm, A. O. (2003). Emotional facilitation of sensory processing in the visual cortex. *Psychol. Sci.* 14, 7–13. doi: 10.1111/1467-9280.01411

Stolarova, M., Keil, A., and Moratti, S. (2006). Modulation of the C1 visual event-related component by conditioned stimuli: evidence for sensory plasticity in early affective perception. *Cereb. Cortex* 16, 876–887. doi: 10.1093/cercor/bhj031

Szmalec, A., Verbruggen, F., Vandierendonck, A., De Baene, W., Verguts, T., and Notebaert, W. (2008). Stimulus ambiguity elicits response conflict. *Neurosci. Lett.* 435, 158–162. doi: 10.1016/j.neulet.2008.02.023

van Veen, V., and Carter, C. S. (2002). The anterior cingulate as a conflict monitor: fMRI and ERP studies. *Physiol. Behav.* 77, 477–482. doi: 10.1016/S0031-9384(02)00930-7

Watson, D., Clark, L. A., and Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *J. Pers. Soc. Psychol.* 54, 1063–1070. doi: 10.1037/0022-3514.54.6.1063

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 14 January 2013; accepted: 26 May 2013; published online: 12 June 2013.

Citation: Schick A, Wessa M, Vollmayr B, Kuehner C and Kanske P (2013) Indirect assessment of an interpretation bias in humans: neurophysiological and behavioral correlates. Front. Hum. Neurosci. 7:272. doi: 10.3389/fnhum.2013.00272

6 General discussion

6.1 Summary

Six studies were conducted to characterize the neural correlates of emotional processing in affective disorders. The first set of studies tested emotion regulation capabilities by engaging participants in two different strategies to influence an emotional response, reappraisal and distraction. The second set of studies looked at the influence that emotion has on cognitive processing by testing performance of a mental arithmetic task while emotional stimuli were presented as distracters. The last study looked at biased information processing with a paradigm that confronted participants with ambiguous situations, thereby allowing for the measurement of more positive or negative interpretation of these situations.

Study 1: How to regulate emotion? Neural networks for reappraisal and distraction. The first study established a paradigm for investigating the neural networks underlying two different emotion regulation strategies, reappraisal and distraction. This was done in healthy individuals. The results show that the paradigm successfully induced emotion in the subjective emotion ratings that participants gave, but also in increased activity in the amygdala for emotional compared to neutral stimuli. Participants reported less emotion when applying either one of the two emotion regulation strategies, which was mirrored by reduced amygdala activity for reappraisal and, even stronger, for distraction. The neural network involved in the downregulation of amygdala activity during reappraisal and distraction included dorsolateral prefrontal, parietal and dorsomedial prefrontal cortices for both strategies. Activity in the orbitofrontal cortex was specific for the reappraisal condition, while distraction yielded stronger and extended activity of parietal cortex and dorsomedial prefrontal cortex, including anterior cingulate cortex. This was verified by the specific connectivity patterns of the amygdala during reappraisal and distraction.

Study 2: Neural correlates of emotion regulation deficits in remitted depression: The influence of regulation strategy, habitual regulation use and emotional valence. The second study applied the paradigm introduced in Study 1 to currently remitted patients with unipolar depression. There were no differences between the patients and their healthy control participants in the subjective ratings of emotional states. However, the patients showed a deficit in downregulating activity in the amygdala when using the reappraisal strategy, but not when applying the distraction strategy. Activity in the regulating control networks was increased for both regulation strategies, potentially indexing a compensatory effect. Interestingly, patients also reported less frequent use

of reappraisal in their everyday life as measured with a questionnaire. These questionnaire reports of habitual reappraisal correlated with the downregulation of amygdala activity when reappraising.

Study 3: Impaired regulation of emotion: Evidence for a vulnerability marker of bipolar disorder. The third study applied the paradigm introduced in Study 1 to euthymic patients with bipolar disorder and unaffected relatives of patients with bipolar disorder. The results show no differences in the subjective emotion ratings between bipolar patients and their controls, but slightly more negative ratings for positive emotional stimuli in unaffected relatives of bipolar disorder patients. Patients and relatives also showed deficient down-regulation of the amygdala when using the reappraisal strategy, but not when applying distraction. Connectivity between the amygdala and orbitofrontal control regions was also altered during reappraisal in patients and controls. The deficits were mirrored in self-reported decreased habitual use of reappraisal as measured with a questionnaire. Similarly to Study 2, these self-reports correlated with the downregulation of amygdala activity when reappraising.

Study 4: Goal-directed behavior under emotional distraction is preserved by enhanced task-specific activation. The fourth study tested the effects of emotional distraction on a mental arithmetic task in healthy individuals. Behaviorally, a slowing in response times was observed, while accuracy of the responses was not impaired. With regard to the neural correlates, the functional localizer task that contrasted mental arithmetic processing with number detection identified a network that was congruent with previously described brain correlates of arithmetic tasks, critically including a widespread cluster in parietal cortex. Activity in this network was significantly increased under emotional distraction. This increase in activity correlated with the behavioral slowing effect.

Study 5: Neural correlates of emotional distractibility in bipolar disorder, unaffected relatives and individuals with hypomanic personality. Study 5 applied the same experimental procedure as Study 4, but tested euthymic patients with bipolar disorder, unaffected relatives of patients with bipolar disorder, individuals scoring high in a questionnaire on hypomanic personality and healthy control groups matched to each of the groups of interest. There were no behavioral differences between the groups in performance of the functional localizer arithmetic task. However, under emotional distraction, all groups showed behavioral slowing, which was significantly increased in bipolar patients. There were no differences in accuracy of performance. The groups did not differ with regard to the neural network activated for mental arithmetic in the functional localizer task. As in study 4, this network consisted of a number of regions, critically involving the parietal cortex bilaterally. Activity in this network was increased under emotional distraction for all groups. Only bipolar patients showed an

enlarged increase in right parietal activity. This activation increase correlated again with the behavioral slowing effect.

Study 6: Indirect assessment of an interpretation bias in humans: Neurophysiological and behavioral correlates. The sixth study tested a paradigm to probe biased information processing in ambiguous situations. The results show that the first training session was able to associate two different reference tones with negative and positive outcomes, as participants learned to press the respective buttons to obtain the positive or avoid the negative outcome. Responses to additional intermediate and, therefore, ambiguous tones were significantly slower. Also, the responses were less clear with regard to the potential outcome. While the tones that were close in frequency to the previously introduced reference tones were still relatively more frequently followed by the most fitting response, the middle tone was approximately equally often responded to with positive and negative button presses. However, the ratio of positive and negative responses to the ambiguous tones, which gives an index of the size of the bias, correlated with the rumination subscale reflective pondering. The ERP results showed larger late positive potentials to the reference compared to the ambiguous tones. Furthermore, the late positive potential was also enlarged for negatively compared to positively interpreted ambiguous tones.

6.2 Implications

Chapter 3 raised five questions that the presented studies aimed to address. The present section revisits each of these questions and evaluates the impact that the results of the studies have on addressing them.

The *first question* targeted voluntary emotion regulation and its neural underpinnings in remitted patients with bipolar disorder and depression. In order to address this question we first validated a paradigm in healthy individuals that allows the direct comparison of two emotion regulation strategies, reappraisal and distraction. As the research on specific emotion regulation greatly has greatly increased over the last years, improving our understanding of their differences and commonalities became more and more important. Our study adds to this by showing that both, reappraisal and distraction, are efficient in down-regulating emotion and concurrent amygdala activity and are implemented through overlapping, but partially distinct control networks, which also showed specific connectivity patterns to the amygdala during application of the strategies (Kanske et al., 2011). In addition to the first previous study on a comparison of strategies (McRae et al., 2009), our study shows that the effects generalize to different types of distraction, working memory and mental arithmetic tasks (Van Dillen et al., 2009) and to emotions of different valence, positive and

negative. An important difference is also the specific experimental design regarding the emotion induction, which occurred only after participants were instructed to regulate any occurring emotion (McRae et al., 2009). Since in our study, the emotion regulation instruction was displayed after the emotional stimulus was presented, it addresses the question whether ongoing emotional responses can still be regulated, which may be particularly critical for clinical populations that also show difficulties in early identification of emotions (Mikhailova, Vladimirova, Iznak, Tsusulkovskaya, & Sushko, 1996). The data differentiate reappraisal and distraction in the amount of amygdala down-regulation, which was stronger during distraction and some regions that were specific to each strategy. For reappraisal this was mainly the orbitofrontal cortex, which is consistent with other studies on cognitive change of emotion (Eippert et al., 2007) and is in line with its involvement in affective reversal learning tasks (Kringelbach & Rolls, 2003) as reappraisal can be described as a self-induced change in emotional responding during constant, unchanged stimulation. Distraction in contrast yielded stronger activation of the anterior cingulate cortex and dorsomedial prefrontal cortex. As distraction is a strategy of attentional control, this nicely fits with the involvement of these regions in executive attentional control as measured with different types of conflict tasks (Botvinick, Cohen, & Carter, 2004; Fan, Flombaum, McCandliss, Thomas, & Posner, 2003). In both, euthymic bipolar and remitted depressed patients, we found that amygdala down-regulation was not as efficient as in the matched healthy control participants when reappraisal was applied, but not during distraction (Kanske et al., 2012), which fits to the stronger and more extended distraction effects in healthy controls. For therapeutic interventions this may indicate that effective distraction can be used as a resource, while reappraisal should be viewed as a special treatment target. The particular relevance is underlined by the correlation of the amygdala regulation deficit with habitual reappraisal as measured in self-reports. A difference between unipolar depression and bipolar disorder lies in the specificity of the regulation deficit to negative emotion in depression, while there were no differences between negative and positive emotional stimuli in bipolar disorder, which fits, of course, to the bipolarity of manic and depressive episodes. The pattern of limbic hyperactivation and altered activity in or connectivity with regions in the regulating control network is in line with the suggestion of impaired prefrontal control over emotion generating regions like the amygdala in affective disorder (Phillips, Ladouceur, et al., 2008). However, it critically specifies the conditions of this impairment. We observed altered amygdala activity in patients and relatives only in the reappraisal condition, not during simple viewing of emotional stimuli. This contrasts other reports of increased amygdala responses to emotion stimuli (Delvecchio et al., 2012; Houenou et al., 2011). However, there are also reports of lacking amygdala group differences, or even blunted amygdala responding to emotional stimuli (Chen et al., 2011; Diener et al., 2012). As these studies did not

explicitly instruct participants how to treat arising emotions it is possible that patients and controls applied regulation differently, potentially in line with their habitual use of emotion regulation (Aldao et al., 2010; Green et al., 2011). By explicitly instructing the use of certain regulation strategies, the present study allowed studying the specific effects of strategies, which could offer an explanation for the discrepant previous results. With regard to unipolar depression, the presented evidence also adds to the literature that the deficit in amygdala regulation is specific to the reappraisal strategy, persists into remission, is related to the reduced habitual use of reappraisal and is specific to negative emotion. In bipolar disorder, the data conforms with two very recent studies on voluntary emotion regulation in bipolar disorder (Morris, Sparks, Mitchell, Weickert, & Green, 2012; Townsend et al., 2013). It also adds to this literature by showing specificity to the reappraisal strategy, persistence into euthymia, the relation to habitual reappraisal use and the lack of differences between positive and negative emotional stimuli. The fact that the deficits in both groups were observed even though none of the patients were still symptomatic, suggests that the deficits are not bound to current illness episodes, but posses trait characteristics.

The *second question* more directly asked about this point whether deficits observed in diagnosed patients with bipolar disorder are a trait- or vulnerability marker of the illness. Therefore, unaffected first-degree relatives of patients with bipolar disorder were tested with the same experimental setup. In comparison to their matched controls, relatives showed the same deficit as bipolar patients in down-regulation of the amygdala through reappraisal, but normal regulation effects when using distraction. Also, direct comparison of the bipolar patient group to the unaffected relatives showed no differences. The presence of these deficits in healthy individuals with increased risk to develop bipolar disorder in the future suggests that they do represent a vulnerability marker for bipolar disorder. As the relatives are not affected by previous manic or depressive episodes, the data indicate that the deficit is not a consequence of but a predisposition for the development of the illness. This is in line with other findings of altered emotional and motivational processing and related ventral-limbic activity in unaffected relatives of patients with bipolar disorder (Linke et al., 2012; Surguladze et al., 2010) and extends these to the regulation of emotion, which has previously only been investigated on a self-report questionnaire level (Green et al., 2011). The fact that the same effects were found in patients and relatives adds to their credibility, as the relatives are unmedicated and the observed impairments seem, therefore, not to be an artifact of medication in bipolar disorder patients.

In contrast to the regulatory influence that cognition can have on emotional processing, the *third question* targeted the distraction effects that emotion can exert on cognitive processes and specifically asked if euthymic bipolar disorder patients show increased emotional distractibility when performing a cognitive task and if such distraction

effects are accompanied by changes in the neural correlates of processing the task at hand. We initially validated a testing procedure in healthy participants that localized the neural network involved in a specific cognitive task, mental arithmetic, in a first step and the studied the influence of emotion on this network by presenting mental arithmetic tasks on emotional distracter images in a second step. The identified network included superior parietal as well as dorsolateral and dorsomedial prefrontal cortex, which is in line with previous mental arithmetic studies (Dehaene, Molko, Cohen, & Wilson, 2004) and the observed behavioral slowing under emotional distraction correlated with increased activity in these regions (Wessa et al., 2013). These data speak to the debate whether emotional distraction yields increased (Blair et al., 2007; Hart et al., 2010; Pereira et al., 2010) or decreased activity (Anticevic et al., 2010; Dolcos et al., 2006; Dolcos & McCarthy, 2006; Mitchell et al., 2008) in 'cognitive' brain regions, in particular since none of the previous studies used independent functional localizers for the respective task-related neural network. The reduced activity found in some studies may, therefore, reflect a different process, potentially the inhibition of task-irrelevant information and the protection against interference (Jha, Fabian, & Aguirre, 2004; Shimamura, 2000). When testing this procedure in euthymic patients with bipolar disorder, we again found increased activity in the task-related network, but the patients showed a significantly greater activity increase in the right parietal cortex than the healthy control participants (Kanske et al., 2013). This activation increase also correlated with the enlarged behavioral distraction effect in the patients. The major relevance of this result lies in linking cognitive deficits in bipolar disorder with emotional dysregulation (Henin et al., 2009; Strakowski et al., 2005). Hyperactivation under emotional distraction has been observed previously, but these studies left it open if the activity increase relates to behavioral deficits as no behavioral impairments were found and as no independent task network identification was undertaken (Bertocci et al., 2012; Deckersbach et al., 2008; Lagopoulos & Malhi, 2007; Malhi et al., 2005; Wessa et al., 2007). As with the emotion regulation deficits discussed above, these alterations were found in currently euthymic bipolar patients, which raises the question if they also represent vulnerability marker characteristics and can already be observed before the actual onset of the disorder.

The *fourth question* addressed this point and asked if exacerbated cognitive deficits under emotional distraction in bipolar disorder are a vulnerability marker or only occur as a consequence of the illness. To this end, the same design as above was tested in two populations at increased risk to develop bipolar disorder, unaffected first-degree relatives of patients with bipolar disorder and healthy individuals with hypomanic personality as defined through self-reports in a questionnaire. None of the two groups showed any differences when compared to carefully matched control groups of healthy participants without the risk factors (Kanske et al., 2013). Also

when compared to the group of bipolar patients, the two at-risk populations showed the same differences to the patients as the controls. That relatives of bipolar patients and participants with hypomanic personality were indistinguishable from their respective comparison counterparts suggests that this deficit is a consequence of the disorder rather than a vulnerability marker. In our study the size of the distraction effect in bipolar patients did not correlate with clinical characteristics such as the number of previous episodes, which indicates that the deficit is present after the experience of at least one illness episode. The described deficit is clinically very important, because cognitive dysfunction, which is, at least partially, caused by increased emotional distractibility, predicts functional recovery (Martinez-Aran, Vieta, Colom, et al., 2004; Martinez-Aran, Vieta, Reinares, et al., 2004). If psychotherapeutic interventions address the exacerbated emotional distractibility, the very low rates of functional recovery in the first two years after an illness episode may be increased (Keck et al., 1998; Tohen et al., 2003).

The *fifth question* also addressed the influence of emotion on cognitive processing and asked if biased cognitive information processing through emotion can be measured indirectly with a paradigm adapted from animal research and if a negative bias is associated with depression related traits. To this end, different tones were associated with positive and negative outcome and the interpretation of ambiguous intermediate tones was taken as an index of biased information processing. In the test sample of healthy individuals, we observed an overall slight positive bias (Cummins & Nistico, 2002) that correlated negatively with interindividual differences in ruminative coping style, specifically in reflective pondering (Schick et al., 2013), a trait that is associated with clinical depression (Joormann, Dkane, & Gotlib, 2006). Participants higher in rumination showed a more negative bias, which is in line with some previous evidence relating rumination to biased processing (Gotlib & Joormann, 2010; Koster, DeLissnyder, Derakshan, & DeRaedt, 2011). The data also add to the literature on biased processing in depression, which mainly applied more direct bias measures and reported partly inconsistent results with an increased (Berna et al., 2011; Lawson et al., 2002) or decreased negative bias in depression (Lawson & MacLeod, 1999). As we also observed a differentiated ERP time-course for physically identical, but differently interpreted ambiguous tones, the paradigm adapted from animal research seems to be also applicable for measuring biased cognitive processing in humans. A further advantage of the design is that it can assess a positive and negative bias alike and is, thus, principally applicable to characterize both, depression and mania in bipolar disorder.

6.3 Critique and conclusions

The present studies have some limitations that give rise to further research question to be addressed in future investigations. This section will briefly review some of these questions and also draw some final conclusions.

A general problem of all the presented studies including clinical groups is that the patients kept receiving antidepressant or mood-stabilizing medication to prevent withdrawal or the emergence of symptoms. This, of course, does not allow testing the pure diease effects, but confounds them with the medication taken. We tried to test the influence of the medication by including a composite measure of medication load (Sackeim, 2001), which has been recommended and used previously (Almeida et al., 2009; Phillips, Travis, Fagiolini, & Kupfer, 2008). Furthermore, with regard to the emotion regulation deficits, they were not only observed in the patient group, but also in the unaffected first-degree relatives of bipolar disorder and healthy individuals with hypomanic personality, which suggests that medication played no role. Nevertheless, future studies should include bigger samples to be able to tease the specific effects of different medications apart.

In all of the described patients studies, currently remitted or euthymic patients were tested. While testing these groups has the advantage that conclusions about the trait characteristics of certain deficits can be drawn, it would also be interesting to test currently symptomatic patients. It is plausible to expect quantitatively stronger impairments in emotion regulation, emotional distractibility and a stronger bias on cognitive processing, but there may also be further qualititative differences. For bipolar patients one of the hypotheses could be that the effects become more valence dependent. In the present studies no differences between positive and negative emotional processing were observed, but currently manic or depressed patients might show such differentiation (Murphy et al., 1999). Also, it could be expected that effects show in subjective emotion ratings, in addition to the neural responses.

A third general issue is that it would be important to probe the specificity of the observed effects to unipolar depression and bipolar disorder. Emotion regulation deficits, for example, have been found in very different mental disorders including borderline personality disorder (Schulze et al., 2011), general anxiety disorder (Salters-Pedneault, Roemer, Tull, Rucker, & Mennin, 2006), social anxiety (Goldin & Gross, 2010), phobia (Hermann et al., 2009) or attention deficit hyperactivity disorder (Walcott & Landau, 2004). It is therefore also discussed as a trans-diagnostic issue (Aldao et al., 2010; Berking et al., 2008) also for the development of psychopathology in childhood and adolescence (Cicchetti, Ackerman, & Izard, 1995). Psychotherapeutic interventions start to adopt emotion regulation modules across disorders (Kovacs et al., 2006; Mennin, 2004; Southam-Gerow & Kendall, 2002). To

probe differences and commonalities across different disorders, future studies should directly compare different matched patient populations.

In the described experiments, the main outcome measures were self-reports and behavioral responses, as well as fMRI and ERP measures. Emotions, however, elicit a whole cascade of further, mainly bodily, responses that were not tested here (Bradley & Lang, 2000). Physiological measures of emotion responsivity such as electrodermal responses or heart rate have been shown to highly correlate with the subjective evaluation of an emotional state (Cuthbert, Bradley, & Lang, 1996) and also with the down-regulation of anxiety (Kalisch et al., 2005), but not necessarily to the regulation of emotion per se (Eippert et al., 2007). Whether peripheral physiological measures are sensitive to the different regulation strategies tested in the studies here, which mechanisms of emotion regulation are reflected by the physiological indicators and if alterations in patients with affective disorders can be differentiated remains unclear and should be investigated in future studies. Such measures could help to characterize the emotional responses more comprehensively. Specifically with regard to the reappraisal strategy it has been shown that it may also be critical to control for eye movements as some participants deploy their attention differently across a given emotional picture stimulus when reappraising (van Reekum et al., 2007). Eye movements only explain part of the observed variance, but might nevertheless also differ between patients and controls in the present studies.

To conclude, the presented studies set out to explore emotion-cognition interactions, their neural correlates and putative alterations in affective disorders. To study the influence of cognition on emotional processing, an emotion regulation paradigm was applied that demonstrated how regulation deficits in patients with unipolar depression and bipolar disorder are present in the control of amygdala activity, which related to habitual emotion regulation use as measured with self-reports. The regulation deficits seem to be a vulnerability marker for bipolar disorder as they already show in healthy individuals at increased risk to develop bipolar disorder. Conversely, the influence of emotion on cognitive processing was tested with an emotional distraction paradigm that showed increased distraction and accompanying task-related hyperactivation in patients with bipolar disorder, but not in individuals at increased risk to develop the disorder, which suggests that it is rather a consequence than a precursor of bipolar disorder. Emotion can also bias cognitive processing as seen in the last study, which demonstrated that such biased processing can be assessed indirectly and that it relates to depression associated rumination traits. The presented evidence shows specific targets for psychotherapeutic treatment that may reduce relapse rates and facilitate psychosocial functional recovery.

7 References

Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature, 372*(6507), 669-672.

Adrian, M., Zeman, J., Erdley, C., Lisa, L., Homan, K., & Sim, L. (2009). Social contextual links to emotion regulation inanadolescent psychiatric inpatientpopulation: do gender and symptomatology matter? . *J Child Psychol Psych, 50*, 1428–1436.

Aggleton, J. (1992). The functional effects of amygdaloid lesions in humans: A comparison with findings from monkeys. In J. Aggleton (Ed.), *The amygdala*. New York and Chichester: Wiley-Liss.

Aldao, A., Nolen-Hoeksema, S., & Schweizer, S. (2010). Emotion-regulation strategies across psychopathology: A meta-analytic review. *Clin Psychol Rev, 30*(2), 217-237.

Almeida, J. R., Versace, A., Hassel, S., Kupfer, D. J., & Phillips, M. L. (2010). Elevated amygdala activity to sad facial expressions: a state marker of bipolar but not unipolar depression. *Biol Psychiatry, 67*(5), 414-421.

Almeida, J. R., Versace, A., Mechelli, A., Hassel, S., Quevedo, K., Kupfer, D. J., & Phillips, M. L. (2009). Abnormal amygdala-prefrontal effective connectivity to happy faces differentiates bipolar from major depression. *Biol Psychiatry, 66*(5), 451-459.

Altman, E. G., Hedeker, D., Peterson, J. L., & Davis, J. M. (1997). The Altman Self-Rating Mania Scale. *Biol Psychiatry, 42*(10), 948-955.

Altshuler, L., Bookheimer, S., Proenza, M. A., Townsend, J., Sabb, F., Firestine, A., Bartzokis, G., Mintz, J., Mazziotta, J., & Cohen, M. S. (2005). Increased amygdala activation during mania: a functional magnetic resonance imaging study. *Am J Psychiatry, 162*(6), 1211-1213.

Altshuler, L., Bookheimer, S., Townsend, J., Proenza, M. A., Sabb, F., Mintz, J., & Cohen, M. S. (2008). Regional brain changes in bipolar I depression: a functional magnetic resonance imaging study. *Bipolar Disord, 10*(6), 708-717.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed. ed.). Arlington, VA: American Psychiatric Publishing.

Anderson, M. H., Hardcastle, C., Munafo, M. R., & Robinson, E. S. (2012). Evaluation of a novel translational task for assessing emotional biases in different species. *Cogn Affect Behav Neurosci, 12*(2), 373-381.

Anticevic, A., Repovs, G., & Barch, D. M. (2010). Resisting emotional interference: brain regions facilitating working memory performance during negative distraction. *Cogn Affect Behav Neurosci, 10*(2), 159-173.

Arts, B., Jabben, N., Krabbendam, L., & van Os, J. (2008). Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives. *Psychol Med, 38*(6), 771-785.

Ashley, V., Vuilleumier, P., & Swick, D. (2004). Time course and specificity of event-related potentials to emotional expressions. *Neuroreport, 15*(1), 211-216.

Austin, M. P., Mitchell, P., & Goodwin, G. M. (2001). Cognitive deficits in depression: possible implications for functional neuropathology. *Br J Psychiatry, 178*, 200-206.

Beauregard, M., Leroux, J. M., Bergman, S., Arzoumanian, Y., Beaudoin, G., Bourgouin, P., & Stip, E. (1998). The functional neuroanatomy of major

depression: an fMRI study using an emotional activation paradigm. *Neuroreport, 9*(14), 3253-3258.

Beauregard, M., Paquette, V., & Levesque, J. (2006). Dysfunction in the neural circuitry of emotional self-regulation in major depressive disorder. *Neuroreport, 17*(8), 843-846.

Beck, A. T. (2008). The evolution of the cognitive model of depression and its neurobiological correlates. *Am J Psychiatry, 165*(8), 969-977.

Beck, A. T., Steer, R. A., & Carbin, M. G. (19888). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clin Psychol Rev, 8*, 77-100.

Berger, H. (1929). Über das Elektroenkephalogramm des Menschen. *Archiv für Psychiatrie und Nervenkrankheiten, 87*, 527-570.

Berking, M., Wupperman, P., Reichardt, A., Pejic, T., Dippel, A., & Znoj, H. (2008). Emotion-regulation skills as a treatment target in psychotherapy. *Behav Res Ther, 46*(11), 1230-1237.

Berna, C., Lang, T. J., Goodwin, G. M., & Holmes, E. A. (2011). Developing a measure of interpretation bias for depressed mood: An ambiguous scenarios test. *Pers Individ Dif, 51*(3), 349-354.

Berns, G. S., Cohen, J. D., & Mintun, M. A. (1997). Brain regions responsive to novelty in the absence of awareness. *Science, 276*(5316), 1272-1275.

Bertocci, M. A., Bebko, G. M., Mullin, B. C., Langenecker, S. A., Ladouceur, C. D., Almeida, J. R., & Phillips, M. L. (2012). Abnormal anterior cingulate cortical activity during emotional n-back task performance distinguishes bipolar from unipolar depressed females. *Psychol Med, 42*(7), 1417-1428.

Blair, K. S., Smith, B. W., Mitchell, D. G., Morton, J., Vythilingam, M., Pessoa, L., Fridberg, D., Zametkin, A., Sturman, D., Nelson, E. E., Drevets, W. C., Pine, D. S., Martin, A., & Blair, R. J. (2007). Modulation of emotion by cognition and cognition by emotion. *Neuroimage, 35*(1), 430-440.

Blanchard, D. C., & Blanchard, R. J. (1972). Innate and conditioned reactions to threat in rats with amygdaloid lesions. *J Comp Physiol Psychol, 81*(2), 281-290.

Bora, E., Yucel, M., & Pantelis, C. (2009). Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *J Affect Disord, 113*(1-2), 1-20.

Botvinick, M. M., Cohen, J. D., & Carter, C. S. (2004). Conflict monitoring and anterior cingulate cortex: an update. *Trends Cogn Sci, 8*(12), 539-546.

Bourke, C., Douglas, K., & Porter, R. (2010). Processing of facial emotion expression in major depression: a review. *Aust N Z J Psychiatry, 44*(8), 681-696.

Bradley, M. M., & Lang, P. J. (2000). Measuring emotion: behavior, feeling and physiology. In R. D. Lane & L. Nadel (Eds.), *Cognitive Neuroscience of Emotion*. Oxford, UK: Oxford University Press.

Burgdorf, J., & Panksepp, J. (2006). The neurobiology of positive emotions. *Neurosci Biobehav Rev, 30*(2), 173-187.

Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci, 4*(6), 215-222.

Butler, G., & Mathews, A. (1983). Cognitive processes in anxiety. *Adv Behav Res Ther, 5*, 51-62.

Campbell-Sills, L., Barlow, D. H., Brown, T. A., & Hofmann, S. G. (2006). Effects of suppression and acceptance on emotional responses of individuals with anxiety and mood disorders. *Behav Res Ther, 44*(9), 1251-1263.

Caton, R. (1875). The electric currents of the brain. *British Medical Journal, 2*, 278.

Chen, C. H., Suckling, J., Lennox, B. R., Ooi, C., & Bullmore, E. T. (2011). A quantitative meta-analysis of fMRI studies in bipolar disorder. *Bipolar Disord, 13*(1), 1-15.

Chepenik, L. G., Cornew, L. A., & Farah, M. J. (2007). The influence of sad mood on cognition. *Emotion, 7*(4), 802-811.

Cicchetti, D., Ackerman, B. P., & Izard, C. E. (1995). Emotions and emotion regulation in developmental psychopathology. *Dev Psychopathol, 7*, 1-10.

Citron, F. M. (2012). Neural correlates of written emotion word processing: a review of recent electrophysiological and hemodynamic neuroimaging studies. *Brain Lang, 122*(3), 211-226.

Clore, G. L., & Ortony, A. (2000). Cognition in emotion: Always, sometimes, or never? In L. Nadel, R. Lane & G. L. Ahern (Eds.), *The cognitive neuroscience of emotion*. New York: Oxford University Press.

Consedine, N. S., Magai, C., & Horton, D. (2005). Ethnic variation in the impact of emotion and emotion regulation on health: a replication and extension. *J Gerontol B Psychol Sci Soc Sci, 60*(4), P165-173.

Cote, S., Gyurak, A., & Levenson, R. W. (2010). The ability to regulate emotion is associated with greater well-being, income, and socioeconomic status. *Emotion, 10*, 923-133.

Craig, A. D. (2009). How do you feel--now? The anterior insula and human awareness. *Nat Rev Neurosci, 10*(1), 59-70.

Cummins, R. A., & Nistico, H. (2002). Maintaining Life Satisfaction: The Role of Positive Cognitive Bias. *J Happiness Stud, 3*(1), 37-69.

Cuthbert, B. N., Bradley, M. M., & Lang, P. J. (1996). Probing picture perception: activation and emotion. *Psychophysiology, 33*(2), 103-111.

Cuthbert, B. N., Schupp, H. T., Bradley, M. M., Birbaumer, N., & Lang, P. J. (2000). Brain potentials in affective picture processing: covariation with autonomic arousal and affective report. *Biol Psychol, 52*(2), 95-111.

Dalgleish, T. (2004). The emotional brain. *Nat Rev Neurosci, 5*(7), 583-589.

Deckersbach, T., Rauch, S. L., Buhlmann, U., Ostacher, M. J., Beucke, J. C., Nierenberg, A. A., Sachs, G., & Dougherty, D. D. (2008). An fMRI investigation of working memory and sadness in females with bipolar disorder: a brief report. *Bipolar Disord, 10*(8), 928-942.

Dehaene, S., Molko, N., Cohen, L., & Wilson, A. J. (2004). Arithmetic and the brain. *Curr Opin Neurobiol, 14*(2), 218-224.

Delvecchio, G., Fossati, P., Boyer, P., Brambilla, P., Falkai, P., Gruber, O., Hietala, J., Lawrie, S. M., Martinot, J. L., McIntosh, A. M., Meisenzahl, E., & Frangou, S. (2012). Common and distinct neural correlates of emotional processing in Bipolar Disorder and Major Depressive Disorder: a voxel-based meta-analysis of functional magnetic resonance imaging studies. *Eur Neuropsychopharmacol, 22*(2), 100-113.

Dichter, G. S., & Tomarken, A. J. (2008). The chronometry of affective startle modulation in unipolar depression. *J Abnorm Psychol, 117*(1), 1-15.

Dichter, G. S., Tomarken, A. J., Shelton, R. C., & Sutton, S. K. (2004). Early- and late-onset startle modulation in unipolar depression. *Psychophysiology, 41*(3), 433-440.

Diener, C., Kuehner, C., Brusniak, W., Ubl, B., Wessa, M., & Flor, H. (2012). A meta-analysis of neurofunctional imaging studies of emotion and cognition in major depression. *Neuroimage, 61*(3), 677-685.

Dolcos, F., Kragel, P., Wang, L., & McCarthy, G. (2006). Role of the inferior frontal cortex in coping with distracting emotions. *Neuroreport, 17*(15), 1591-1594.

Dolcos, F., LaBar, K. S., & Cabeza, R. (2004). Interaction between the amygdala and the medial temporal lobe memory system predicts better memory for emotional events. *Neuron, 42*(5), 855-863.

Dolcos, F., & McCarthy, G. (2006). Brain systems mediating cognitive interference by emotional distraction. *J Neurosci, 26*(7), 2072-2079.

Drabant, E. M., McRae, K., Manuck, S. B., Hariri, A. R., & Gross, J. J. (2009). Individual differences in typical reappraisal use predict amygdala and prefrontal responses. *Biol Psychiatry, 65*(5), 367-373.

Drevets, W. C., Price, J. L., Bardgett, M. E., Reich, T., Todd, R. D., & Raichle, M. E. (2002). Glucose metabolism in the amygdala in depression: relationship to diagnostic subtype and plasma cortisol levels. *Pharmacol Biochem Behav, 71*(3), 431-447.

Drevets, W. C., Videen, T. O., Price, J. L., Preskorn, S. H., Carmichael, S. T., & Raichle, M. E. (1992). A functional anatomical study of unipolar depression. *J Neurosci, 12*(9), 3628-3641.

Eckblad, M., & Chapman, L. J. (1986). Development and validation of a scale for hypomanic personality. *J Abnorm Psychol, 95*(3), 214-222.

Egloff, B., Schmukle, S. C., Burns, L. R., & Schwerdtfeger, A. (2006). Spontaneous emotion regulation during evaluated speaking tasks: associations with

negative affect, anxiety expression, memory, and physiological responding. *Emotion, 6*(3), 356-366.

Eippert, F., Veit, R., Weiskopf, N., Erb, M., Birbaumer, N., & Anders, S. (2007). Regulation of emotional responses elicited by threat-related stimuli. *Hum Brain Mapp, 28*(5), 409-423.

Enkel, T., Gholizadeh, D., von Bohlen Und Halbach, O., Sanchis-Segura, C., Hurlemann, R., Spanagel, R., Gass, P., & Vollmayr, B. (2010). Ambiguous-cue interpretation is biased under stress- and depression-like states in rats. *Neuropsychopharmacology, 35*(4), 1008-1015.

Erk, S., Mikschl, A., Stier, S., Ciaramidaro, A., Gapp, V., Weber, B., & Walter, H. (2010). Acute and sustained effects of cognitive emotion regulation in major depression. *J Neurosci, 30*(47), 15726-15734.

Etkin, A., Egner, T., & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends Cogn Sci, 15*(2), 85-93.

Fan, J., Flombaum, J. I., McCandliss, B. D., Thomas, K. M., & Posner, M. I. (2003). Cognitive and brain consequences of conflict. *Neuroimage, 18*(1), 42-57.

Foland-Ross, L. C., Bookheimer, S. Y., Lieberman, M. D., Sugar, C. A., Townsend, J. D., Fischer, J., Torrisi, S., Penfold, C., Madsen, S. K., Thompson, P. M., & Altshuler, L. L. (2012). Normal amygdala activation but deficient ventrolateral prefrontal activation in adults with bipolar disorder during euthymia. *Neuroimage, 59*(1), 738-744.

Forgas, J. P. (1998). On feeling good and getting your way: mood effects on negotiator cognition and bargaining strategies. *J Pers Soc Psychol, 74*(3), 565-577.

Forgas, J. P., & Bower, G. H. (1987). Mood effects on person-perception judgments. *J Pers Soc Psychol, 53*(1), 53-60.

Frijda, N. H. (1994). Varieties of affect: Emotions and episodes, moods and sentiments. In P. Ekman & R. J. Davidson (Eds.), *The nature of emotion: Fundamental questions*. Oxford and New York: Oxford University Press.

Frodl, T., Scheuerecker, J., Albrecht, J., Kleemann, A. M., Muller-Schunk, S., Koutsouleris, N., Moller, H. J., Bruckmann, H., Wiesmann, M., & Meisenzahl, E. (2009). Neuronal correlates of emotional processing in patients with major depression. *World J Biol Psychiatry, 10*(3), 202-208.

Gall, S., Kerschreiter, R., & Mojzisch, A. (2002). *Handbuch Biopsychologie und Neurowissenschaften*. Bern: Huber.

Gentil, A. F., Eskandar, E. N., Marci, C. D., Evans, K. C., & Dougherty, D. D. (2009). Physiological responses to brain stimulation during limbic surgery: further evidence of anterior cingulate modulation of autonomic arousal. *Biol Psychiatry, 66*(7), 695-701.

Giakoumaki, S. G., Bitsios, P., Frangou, S., Roussos, P., Aasen, I., Galea, A., & Kumari, V. (2010). Low baseline startle and deficient affective startle modulation in remitted bipolar disorder patients and their unaffected siblings. *Psychophysiology, 47*(4), 659-668.

Gilboa, E., & Gotlib, I. H. (1997). Cognitive biases and affect persistence in previously dysphoric and never-dysphoric individuals. *Cogn Emo, 11*, 517-538.

Goldin, P. R., & Gross, J. J. (2010). Effects of mindfulness-based stress reduction (MBSR) on emotion regulation in social anxiety disorder. *Emotion, 10*(1), 83-91.

Gotlib, I. H., & Joormann, J. (2010). Cognition and depression: current status and future directions. *Annu Rev Clin Psychol, 6*, 285-312.

Gottesman, II, & Gould, T. D. (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry, 160*(4), 636-645.

Green, M. J., Lino, B. J., Hwang, E. J., Sparks, A., James, C., & Mitchell, P. B. (2011). Cognitive regulation of emotion in bipolar I disorder and unaffected biological relatives. *Acta Psychiatr Scand, 124*(4), 307-316.

Grillon, C., Ameli, R., Woods, S. W., Merikangas, K., & Davis, M. (1991). Fear-potentiated startle in humans: effects of anticipatory anxiety on the acoustic blink reflex. *Psychophysiology, 28*(5), 588-595.

Gross, J. J. (1999). Emotion regulation: Past, present, future. *Cogn Emo, 13*, 551-573.

Gross, J. J. (2002). Emotion regulation: affective, cognitive, and social consequences. *Psychophysiology, 39*(3), 281-291.

Gualtieri, C. T., & Morgan, D. W. (2008). The frequency of cognitive impairment in patients with anxiety, depression, and bipolar disorder: an unaccounted source of variance in clinical trials. *J Clin Psychiatry, 69*(7), 1122-1130.

Haber, S. N. (2011). Neuroanatomy of Reward: A View from the Ventral Striatum. In J. A. Gottfried (Ed.), *Neurobiology of Sensation and Reward*. Boca Raton (FL).

Haber, S. N., & Knutson, B. (2010). The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology, 35*(1), 4-26.

Hajcak, G., MacNamara, A., & Olvet, D. M. (2010). Event-related potentials, emotion, and emotion regulation: an integrative review. *Dev Neuropsychol, 35*(2), 129-155.

Hamann, S. (2001). Cognitive and neural mechanisms of emotional memory. *Trends Cogn Sci, 5*(9), 394-400.

Hamilton, M. (1960). A rating scale for depression. *J Neurol Neurosurg Psychiatry, 23*, 56-62.

Hamm, A. O., Weike, A. I., Schupp, H. T., Treig, T., Dressel, A., & Kessler, C. (2003). Affective blindsight: intact fear conditioning to a visual cue in a cortically blind patient. *Brain, 126*(Pt 2), 267-275.

Harding, E. J., Paul, E. S., & Mendl, M. (2004). Animal behaviour: cognitive bias and affective state. *Nature, 427*(6972), 312.

Hart, S. J., Green, S. R., Casp, M., & Belger, A. (2010). Emotional priming effects during Stroop task performance. *Neuroimage, 49*(3), 2662-2670.

Henin, A., Micco, J. A., Wozniak, J., Briesch, J. M., Narayan, A. J., & Hirshfeld-Becker, D. R. (2009). Neurocognitive Functioning in Bipolar Disorder. *Clin Psychol Sci Pract, 16*(2), 231-250.

Hermann, A., Schafer, A., Walter, B., Stark, R., Vaitl, D., & Schienle, A. (2009). Emotion regulation in spider phobia: role of the medial prefrontal cortex. *Soc Cogn Affect Neurosci, 4*(3), 257-267.

Houenou, J., Frommberger, J., Carde, S., Glasbrenner, M., Diener, C., Leboyer, M., & Wessa, M. (2011). Neuroimaging-based markers of bipolar disorder: evidence from two meta-analyses. *J Affect Disord, 132*(3), 344-355.

Ingram, R. E., Bernet, C. Z., & McLaughlin, S. C. (1994). Attentional allocation processes in individuals at risk for depression. *Cogn Ther Res, 18*, 317-332.

Isaac, L., Vrijsen, J. N., Eling, P., van Oostrom, I., Speckens, A., & Becker, E. S. (2012). Verbal and facial-emotional Stroop tasks reveal specific attentional interferences in sad mood. *Brain Behav, 2*(1), 74-83.

Jha, A. P., Fabian, S. A., & Aguirre, G. K. (2004). The role of prefrontal cortex in resolving distractor interference. *Cogn Affect Behav Neurosci, 4*(4), 517-527.

Johnstone, T., van Reekum, C. M., Urry, H. L., Kalin, N. H., & Davidson, R. J. (2007). Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. *J Neurosci, 27*(33), 8877-8884.

Joormann, J., Dkane, M., & Gotlib, I. H. (2006). Adaptive and maladaptive components of rumination? Diagnostic specificity and relation to depressive biases. *Behav Ther, 37*, 269-280.

Kaestner, E. J., & Polich, J. (2011). Affective recognition memory processing and event-related brain potentials. *Cogn Affect Behav Neurosci, 11*(2), 186-198.

Kalisch, R. (2009). The functional neuroanatomy of reappraisal: time matters. *Neurosci Biobehav Rev, 33*(8), 1215-1226.

Kalisch, R., Wiech, K., Critchley, H. D., & Dolan, R. J. (2006). Levels of appraisal: a medial prefrontal role in high-level appraisal of emotional material. *Neuroimage, 30*(4), 1458-1466.

Kalisch, R., Wiech, K., Critchley, H. D., Seymour, B., O'Doherty, J. P., Oakley, D. A., Allen, P., & Dolan, R. J. (2005). Anxiety reduction through detachment: subjective, physiological, and neural effects. *J Cogn Neurosci, 17*, 874-883.

Kanske, P. (2012). On the influence of emotion on conflict processing. *Front Integr Neurosci, 6*, 42.

Kanske, P., Heissler, J., Schonfelder, S., Bongers, A., & Wessa, M. (2011). How to regulate emotion? Neural networks for reappraisal and distraction. *Cereb Cortex, 21*(6), 1379-1388.

Kanske, P., Heissler, J., Schonfelder, S., Forneck, J., & Wessa, M. (2013). Neural Correlates of Emotional Distractibility in Bipolar Disorder Patients, Unaffected Relatives, and Individuals With Hypomanic Personality. *Am J Psychiatry, 170*, 1487-1496.

Kanske, P., Heissler, J., Schonfelder, S., & Wessa, M. (2012). Neural correlates of emotion regulation deficits in remitted depression: the influence of regulation strategy, habitual regulation use, and emotional valence. *Neuroimage, 61*(3), 686-693.

Kanske, P., & Kotz, S. A. (2007). Concreteness in emotional words: ERP evidence from a hemifield study. *Brain Res, 1148*, 138-148.

Kanske, P., & Kotz, S. A. (2010). Modulation of early conflict processing: N200 responses to emotional words in a flanker task. *Neuropsychologia, 48*(12), 3661-3664.

Kanske, P., & Kotz, S. A. (2011a). Conflict processing is modulated by positive emotion: ERP data from a flanker task. *Behav Brain Res, 219*(2), 382-386.

Kanske, P., & Kotz, S. A. (2011b). Emotion speeds up conflict resolution: a new role for the ventral anterior cingulate cortex? *Cereb Cortex, 21*(4), 911-919.

Kanske, P., & Kotz, S. A. (2011c). Emotion triggers executive attention: anterior cingulate cortex and amygdala responses to emotional words in a conflict task. *Hum Brain Mapp, 32*(2), 198-208.

Kanske, P., & Kotz, S. A. (2011d). Positive emotion speeds up conflict processing: ERP responses in an auditory Simon task. *Biol Psychol, 87*(1), 122-127.

Kanske, P., Schonfelder, S., Forneck, J., & Wessa, M. (in press). Impaired regulation of emotion: Neural correlates of reappraisal and distraction in bipolar disorder and unaffected relatives. *Transl Psychiatry*.

Keck, P. E., Jr., McElroy, S. L., Strakowski, S. M., West, S. A., Sax, K. W., Hawkins, J. M., Bourne, M. L., & Haggard, P. (1998). 12-month outcome of patients with bipolar disorder following hospitalization for a manic or mixed episode. *Am J Psychiatry, 155*(5), 646-652.

Keltner, D., & Gross, J. J. (1999). Functional accounts of emotions. *Cogn Emo, 13*(5), 467-480.

Kluver, H., & Bucy, P. C. (1937). "Psychic blindness" and other symptoms following bilateral temporal lobectomy. *Am J Physiol, 119*, 254-284.

Koster, E. H. W., De Raedt, R., Goeleven, E., Franck, E., & Crombez, G. (2005). Mood-congruent attentional bias in dysphoria: maintained attention to and impaired disengagement from negative information. *Emotion, 5*(4), 446-455.

Koster, E. H. W., DeLissnyder, E., Derakshan, N., & DeRaedt, R. (2011). Understanding depressive rumination from a cognitive science perspective: the impaired disengagement hypothesis. *Clin Psychol Rev, 31*, 138-145.

Kovacs, M., Sherrill, J., George, C. J., Pollock, M., Tumuluru, R. V., & Ho, V. (2006). Contextual emotion-regulation therapy for childhood depression: description and pilot testing of a new intervention. *J Am Acad Child Adolesc Psychiatry, 45*(8), 892-903.

Kringelbach, M. L., & Rolls, E. T. (2003). Neural correlates of rapid reversal learning in a simple model of human social interaction. *Neuroimage, 20*(2), 1371-1383.

Kwapil, T. R., Miller, M. B., Zinser, M. C., Chapman, L. J., Chapman, J., & Eckblad, M. (2000). A longitudinal study of high scorers on the hypomanic personality scale. *J Abnorm Psychol, 109*(2), 222-226.

Lagopoulos, J., & Malhi, G. S. (2007). A functional magnetic resonance imaging study of emotional Stroop in euthymic bipolar disorder. *Neuroreport, 18*(15), 1583-1587.

Lawson, C., & MacLeod, C. (1999). Depression and the interpretation of ambiguity. *Behav Res Ther, 37*(5), 463-474.

Lawson, C., MacLeod, C., & Hammond, G. (2002). Interpretation revealed in the blink of an eye: depressive bias in the resolution of ambiguity. *J Abnorm Psychol, 111*(2), 321-328.

Leboyer, M., Bellivier, F., Nosten-Bertrand, M., Jouvent, R., Pauls, D., & Mallet, J. (1998). Psychiatric genetics: search for phenotypes. *Trends Neurosci, 21*(3), 102-105.

LeDoux, J. E. (1995). Emotion: clues from the brain. *Annu Rev Psychol, 46*, 209-235.

LeDoux, J. E. (2007). The amygdala. *Curr Biol, 17*(20), R868-874.

Leonard, C. M., Rolls, E. T., Wilson, F. A., & Baylis, G. C. (1985). Neurons in the amygdala of the monkey with responses selective for faces. *Behav Brain Res, 15*(2), 159-176.

Levin, R. L., Heller, W., Mohanty, A., Herrington, J. D., & Miller, G. A. (2007). Cognitive deficits in depression and functional specificity of regional brain activity. *Cogn Ther Res, 31*, 211-233.

Levitt, J. T., Brown, T. A., Orsillo, S. M., & Barlow, D. H. (2004). The effects of acceptance versus suppression of emotion on subjective and psychophysiological response to carbon dioxide challenge in patients with panic disorder. *Behav Ther, 35*, 747-766.

Lieberman, M. D., Eisenberger, N. I., Crockett, M. J., Tom, S. M., Pfeifer, J. H., & Way, B. M. (2007). Putting feelings into words: affect labeling disrupts amygdala activity in response to affective stimuli. *Psychol Sci, 18*(5), 421-428.

Linke, J., King, A. V., Rietschel, M., Strohmaier, J., Hennerici, M., Gass, A., Meyer-Lindenberg, A., & Wessa, M. (2012). Increased medial orbitofrontal and amygdala activation: evidence for a systems-level endophenotype of bipolar I disorder. *Am J Psychiatry, 169*(3), 316-325.

Lippert, M. T., Steudel, T., Ohl, F., Logothetis, N. K., & Kayser, C. (2010). Coupling of neural activity and fMRI-BOLD in the motion area MT. *Magn Reson Imaging, 28*(8), 1087-1094.

Liu, J., Blond, B. N., van Dyck, L. I., Spencer, L., Wang, F., & Blumberg, H. P. (2012). Trait and state corticostriatal dysfunction in bipolar disorder during emotional face processing. *Bipolar Disord, 14*(4), 432-441.

Lovibond, P. F., & Lovibond, S. H. (1995). The structure of negative emotional states: comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. *Behav Res Ther, 33*(3), 335-343.

M'Bailara, K., Demotes-Mainard, J., Swendsen, J., Mathieu, F., Leboyer, M., & Henry, C. (2009). Emotional hyper-reactivity in normothymic bipolar patients. *Bipolar Disord, 11*(1), 63-69.

Malhi, G. S., Ivanovski, B., Hadzi-Pavlovic, D., Mitchell, P. B., Vieta, E., & Sachdev, P. (2007). Neuropsychological deficits and functional impairment in bipolar depression, hypomania and euthymia. *Bipolar Disord, 9*(1-2), 114-125.

Malhi, G. S., Lagopoulos, J., Sachdev, P. S., Ivanovski, B., & Shnier, R. (2005). An emotional Stroop functional MRI study of euthymic bipolar disorder. *Bipolar Disord, 7 Suppl 5*, 58-69.

Malhi, G. S., Lagopoulos, J., Ward, P. B., Kumari, V., Mitchell, P. B., Parker, G. B., Ivanovski, B., & Sachdev, P. (2004). Cognitive generation of affect in bipolar depression: an fMRI study. *Eur J Neurosci, 19*(3), 741-754.

Martinez-Aran, A., Vieta, E., Colom, F., Torrent, C., Sanchez-Moreno, J., Reinares, M., Benabarre, A., Goikolea, J. M., Brugue, E., Daban, C., & Salamero, M. (2004). Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. *Bipolar Disord, 6*(3), 224-232.

Martinez-Aran, A., Vieta, E., Reinares, M., Colom, F., Torrent, C., Sanchez-Moreno, J., Benabarre, A., Goikolea, J. M., Comes, M., & Salamero, M. (2004). Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. *Am J Psychiatry, 161*(2), 262-270.

Mathews, A., & MacLeod, C. (1994). Cognitive approaches to emotion and emotional disorders. *Annu Rev Psychol, 45*, 25–50.

Mathews, A., & MacLeod, C. (2005). Cognitive vulnerability to emotional disorders. *Annu Rev Clin Psychol, 1*, 167-195.

McHaffie, J. G., Stanford, T. R., Stein, B. E., Coizet, V., & Redgrave, P. (2005). Subcortical loops through the basal ganglia. *Trends Neurosci, 28*(8), 401-407.

McRae, K., Hughes, B., Chopra, S., Gabrieli, J. D., Gross, J. J., & Ochsner, K. N. (2009). The Neural Bases of Distraction and Reappraisal. *J Cogn Neurosci*.

Mennin, D. S. (2004). Emotion regulation therapy for generalized anxiety disorder. *Clin Psychol Psychother, 11*, 17-29.

Meunier, M., Bachevalier, J., Murray, E. A., Malkova, L., & Mishkin, M. (1999). Effects of aspiration versus neurotoxic lesions of the amygdala on emotional responses in monkeys. *Eur J Neurosci, 11*(12), 4403-4418.

Mikhailova, E. S., Vladimirova, T. V., Iznak, A. F., Tsusulkovskaya, E. J., & Sushko, N. V. (1996). Abnormal recognition of facial expression of emotions in depressed patients with major depression disorder and schizotypal personality disorder. *Biol Psychiatry, 40*(8), 697-705.

Mitchell, D. G., Luo, Q., Mondillo, K., Vythilingam, M., Finger, E. C., & Blair, R. J. (2008). The interference of operant task performance by emotional distracters: an antagonistic relationship between the amygdala and frontoparietal cortices. *Neuroimage, 40*(2), 859-868.

Morris, J. S., Ohman, A., & Dolan, R. J. (1999). A subcortical pathway to the right amygdala mediating "unseen" fear. *Proc Natl Acad Sci U S A, 96*(4), 1680-1685.

Morris, R. W., Sparks, A., Mitchell, P. B., Weickert, C. S., & Green, M. J. (2012). Lack of cortico-limbic coupling in bipolar disorder and schizophrenia during emotion regulation. *Transl Psychiatry, 2*, e90.

Murphy, F. C., Sahakian, B. J., Rubinsztein, J. S., Michael, A., Rogers, R. D., Robbins, T. W., & Paykel, E. S. (1999). Emotional bias and inhibitory control processes in mania and depression. *Psychol Med, 29*(6), 1307-1321.

Nair, D. G. (2005). About being BOLD. *Brain Res Brain Res Rev, 50*(2), 229-243.

Ochsner, K. N., Bunge, S. A., Gross, J. J., & Gabrieli, J. D. (2002). Rethinking feelings: an FMRI study of the cognitive regulation of emotion. *J Cogn Neurosci, 14*(8), 1215-1229.

Ochsner, K. N., & Gross, J. J. (2005). The cognitive control of emotion. *Trends Cogn Sci, 9*(5), 242-249.

Ogawa, S., Lee, T. M., Nayak, A. S., & Glynn, P. (1990). Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. *Magn Reson Med, 14*(1), 68-78.

Olofsson, J. K., Nordin, S., Sequeira, H., & Polich, J. (2008). Affective picture processing: an integrative review of ERP findings. *Biol Psychol, 77*(3), 247-265.

Padmala, S., & Pessoa, L. (2011). Reward reduces conflict by enhancing attentional control and biasing visual cortical processing. *J Cogn Neurosci, 23*(11), 3419-3432.

Paelecke-Habermann, Y., Pohl, J., & Leplow, B. (2005). Attention and executive functions in remitted major depression patients. *J Affect Disord, 89*(1-3), 125-135.

Page, A. C., Hooke, G. R., & Morrison, D. L. (2007). Psychometric properties of the Depression Anxiety Stress Scales (DASS) in depressed clinical samples. *Br J Clin Psychol, 46*(Pt 3), 283-297.

Pagnoni, G., Zink, C. F., Montague, P. R., & Berns, G. S. (2002). Activity in human ventral striatum locked to errors of reward prediction. *Nat Neurosci, 5*(2), 97-98.

Pereira, M. G., de Oliveira, L., Erthal, F. S., Joffily, M., Mocaiber, I. F., Volchan, E., & Pessoa, L. (2010). Emotion affects action: Midcingulate cortex as a pivotal node of interaction between negative emotion and motor signals. *Cogn Affect Behav Neurosci, 10*(1), 94-106.

Pessoa, L. (2008). On the relationship between emotion and cognition. *Nat Rev Neurosci, 9*(2), 148-158.

Pessoa, L., & Adolphs, R. (2010). Emotion processing and the amygdala: from a 'low road' to 'many roads' of evaluating biological significance. *Nat Rev Neurosci, 11*(11), 773-783.

Phan, K. L., Wager, T., Taylor, S. F., & Liberzon, I. (2002). Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage, 16*(2), 331-348.

Phillips, M. L., Ladouceur, C. D., & Drevets, W. C. (2008). A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. *Mol Psychiatry, 13*(9), 829, 833-857.

Phillips, M. L., Travis, M. J., Fagiolini, A., & Kupfer, D. J. (2008). Medication effects in neuroimaging studies of bipolar disorder. *Am J Psychiatry, 165*(3), 313-320.

Ray, R. D., McRae, K., Ochsner, K. N., & Gross, J. J. (2010). Cognitive reappraisal of negative affect: converging evidence from EMG and self-report. *Emotion, 10*(4), 587-592.

Richter, S. H., Schick, A., Hoyer, C., Lankisch, K., Gass, P., & Vollmayr, B. (2012). A glass full of optimism: enrichment effects on cognitive bias in a rat model of depression. *Cogn Affect Behav Neurosci, 12*(3), 527-542.

Rickard, T. C., Romero, S. G., Basso, G., Wharton, C., Flitman, S., & Grafman, J. (2000). The calculating brain: an fMRI study. *Neuropsychologia, 38*(3), 325-335.

Rozenkrants, B., & Polich, J. (2008). Affective ERP processing in a visual oddball task: arousal, valence, and gender. *Clin Neurophysiol, 119*(10), 2260-2265.

Sackeim, H. A. (2001). The definition and meaning of treatment-resistant depression. *J Clin Psychiatry, 62 Suppl 16*, 10-17.

Salters-Pedneault, K., Roemer, L., Tull, M. T., Rucker, L., & Mennin, D. S. (2006). Evidence of broad deficits in emotion regulation associated with chronic worry and generalized anxiety disorder. *Cogn Ther Res, 30*, 469-480.

Schacht, A., Adler, N., Chen, P., Guo, T., & Sommer, W. (2012). Association with positive outcome induces early effects in event-related brain potentials. *Biol Psychol, 89*(1), 130-136.

Scherer, K. R. (1994). Emotion serves to decouple stimulus and response. In P. Ekman & R. J. Davidson (Eds.), *The nature of emotion: Fundamental questions* New York and Oxford: Oxford University Press.

Schick, A., Wessa, M., Vollmayr, B., Kuehner, C., & Kanske, P. (2013). Indirect assessment of an interpretation bias in humans: neurophysiological and behavioral correlates. *Front Hum Neurosci, 7*, 272.

Schirmer, A., & Kotz, S. A. (2006). Beyond the right hemisphere: brain mechanisms mediating vocal emotional processing. *Trends Cogn Sci, 10*(1), 24-30.

Schulze, L., Domes, G., Kruger, A., Berger, C., Fleischer, M., Prehn, K., Schmahl, C., Grossmann, A., Hauenstein, K., & Herpertz, S. C. (2011). Neuronal correlates of cognitive reappraisal in borderline patients with affective instability. *Biol Psychiatry, 69*(6), 564-573.

Segal, Z. V., Kennedy, S., Gemar, M., Hood, K., Pedersen, R., & Buis, T. (2006). Cognitive reactivity to sad mood provocation and the prediction of depressive relapse. *Arch Gen Psychiatry, 63*(7), 749-755.

Sergerie, K., Chochol, C., & Armony, J. L. (2008). The role of the amygdala in emotional processing: a quantitative meta-analysis of functional neuroimaging studies. *Neurosci Biobehav Rev, 32*(4), 811-830.

Sheline, Y. I., Barch, D. M., Donnelly, J. M., Ollinger, J. M., Snyder, A. Z., & Mintun, M. A. (2001). Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biol Psychiatry, 50*(9), 651-658.

Shimamura, A. P. (2000). The role of the prefrontal cortex in dynamic filtering. *Psychobiol, 28*, 207-218.

Siegle, G. J., Thompson, W., Carter, C. S., Steinhauer, S. R., & Thase, M. E. (2007). Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. *Biol Psychiatry, 61*(2), 198-209.

Singer, T. (2012). The past, present and future of social neuroscience: a European perspective. *Neuroimage, 61*(2), 437-449.

Southam-Gerow, M. A., & Kendall, P. C. (2002). Emotion regulation and understanding: implications for child psychopathology and therapy. *Clin Psychol Rev, 22*(2), 189-222.

Strakowski, S. M., Delbello, M. P., & Adler, C. M. (2005). The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. *Mol Psychiatry, 10*(1), 105-116.

Surguladze, S. A., Brammer, M. J., Keedwell, P., Giampietro, V., Young, A. W., Travis, M. J., Williams, S. C., & Phillips, M. L. (2005). A differential pattern of neural response toward sad versus happy facial expressions in major depressive disorder. *Biol Psychiatry, 57*(3), 201-209.

Surguladze, S. A., Marshall, N., Schulze, K., Hall, M. H., Walshe, M., Bramon, E., Phillips, M. L., Murray, R. M., & McDonald, C. (2010). Exaggerated neural response to emotional faces in patients with bipolar disorder and their first-degree relatives. *Neuroimage, 53*(1), 58-64.

Sweeney, J. A., Kmiec, J. A., & Kupfer, D. J. (2000). Neuropsychologic impairments in bipolar and unipolar mood disorders on the CANTAB neurocognitive battery. *Biol Psychiatry, 48*(7), 674-684.

Tamietto, M., & de Gelder, B. (2010). Neural bases of the non-conscious perception of emotional signals. *Nat Rev Neurosci, 11*(10), 697-709.

Tamietto, M., Pullens, P., de Gelder, B., Weiskrantz, L., & Goebel, R. (2012). Subcortical connections to human amygdala and changes following destruction of the visual cortex. *Curr Biol, 22*(15), 1449-1455.

Terzian, H., & Ore, G. D. (1955). Syndrome of Kluver and Bucy; reproduced in man by bilateral removal of the temporal lobes. *Neurology, 5*(6), 373-380.

Timbremont, B., & Braet, C. (2004). Cognitive vulnerability in remitted depressed children and adolescents. *Behav Res Ther, 42*(4), 423-437.

Tohen, M., Zarate, C. A., Jr., Hennen, J., Khalsa, H. M., Strakowski, S. M., Gebre-Medhin, P., Salvatore, P., & Baldessarini, R. J. (2003). The McLean-Harvard First-Episode Mania Study: prediction of recovery and first recurrence. *Am J Psychiatry, 160*(12), 2099-2107.

Townsend, J. D., Torrisi, S. J., Lieberman, M. D., Sugar, C. A., Bookheimer, S. Y., & Altshuler, L. L. (2013). Frontal-amygdala connectivity alterations during emotion downregulation in bipolar I disorder. *Biol Psychiatry, 73*(2), 127-135.

Turner, R., von Kienlin, M., Moonen, C. T., & van Zijl, P. C. (1990). Single-shot localized echo-planar imaging (STEAM-EPI) at 4.7 tesla. *Magn Reson Med, 14*(2), 401-408.

Van Dillen, L. F., Heslenfeld, D. J., & Koole, S. L. (2009). Tuning down the emotional brain: an fMRI study of the effects of cognitive load on the processing of affective images. *Neuroimage, 45*(4), 1212-1219.

van Reekum, C. M., Johnstone, T., Urry, H. L., Thurow, M. E., Schaefer, H. S., Alexander, A. L., & Davidson, R. J. (2007). Gaze fixations predict brain activation during the voluntary regulation of picture-induced negative affect. *Neuroimage, 36*(3), 1041-1055.

Vuilleumier, P., & Pourtois, G. (2007). Distributed and interactive brain mechanisms during emotion face perception: evidence from functional neuroimaging. *Neuropsychologia, 45*(1), 174-194.

Wadlinger, H. A., & Isaacowitz, D. M. (2006). Positive mood broadens visual attention to positive stimuli. *Motiv Emot, 30*(1), 87-99.

Wager, T. D., Davidson, M. L., Hughes, B. L., Lindquist, M. A., & Ochsner, K. N. (2008). Prefrontal-subcortical pathways mediating successful emotion regulation. *Neuron, 59*(6), 1037-1050.

Walcott, C. M., & Landau, S. (2004). The relation between disinhibition and emotion regulation in boys with attention deficit hyperactivity disorder. *J Clin Child Adolesc Psychol, 33*, 772-782.

Walter, H., von Kalckreuth, A., Schardt, D., Stephan, A., Goschke, T., & Erk, S. (2009). The temporal dynamics of voluntary emotion regulation. *PLoS One, 4*(8), e6726.

Weiskrantz, L. (1956). Behavioral changes associated with ablation of the amygdaloid complex in monkeys. *J Comp Physiol Psychol, 49*(4), 381-391.

Wessa, M., Heissler, J., Schonfelder, S., & Kanske, P. (2013). Goal-directed behavior under emotional distraction is preserved by enhanced task-specific activation. *Soc Cogn Affect Neurosci, 8*(3), 305-312.

Wessa, M., Houenou, J., Paillere-Martinot, M. L., Berthoz, S., Artiges, E., Leboyer, M., & Martinot, J. L. (2007). Fronto-striatal overactivation in euthymic bipolar patients during an emotional go/nogo task. *Am J Psychiatry, 164*(4), 638-646.

Whalen, P. J., & Phelps, E. A. (2009). *The human amygdala*. New York: Guilford Press.

Williams, J. B. (2001). Standardizing the Hamilton Depression Rating Scale: past, present, and future. *Eur Arch Psychiatry Clin Neurosci, 251 Suppl 2*, II6-12.

Willner, P. (1997). Validity, reliability and utility of the chronic mild stress model of depression: a 10-year review and evaluation. *Psychopharmacology (Berl), 134*(4), 319-329.

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry, 133*, 429-435.

Zurita, A., Martijena, I., Cuadra, G., Brandao, M. L., & Molina, V. (2000). Early exposure to chronic variable stress facilitates the occurrence of anhedonia and enhanced emotional reactions to novel stressors: reversal by naltrexone pretreatment. *Behav Brain Res, 117*(1-2), 163-171.

Acknowledgments

I am thankful for the support of many people. Without them the studies reported here could not have been carried out. In particular I would like to thank

Michèle Wessa, first and foremost, who not only enabled me to carry out this habilitation in the first place, but who continuously and fully supported me throughout the PostDoc, including my clinical work. I am truly grateful and still an admirer of here abundance of energy that makes people fly.

Herta Flor for her support for the projects reported here as Scientific Director of the Department of Cognitive and Clinical Neuroscience at the Central Institute of Mental Health.

Janine Heissler, Sandra Schönfelder and Johanna Forneck for the effective and enjoyable time we spent as “Emmys” and for all their contributions to the studies.

All my colleagues at the Central Institute of Mental Health, in particular Sandra Kamping, Patric Meyer, Carsten Diener, Karin Rosenkranz for all the discussions, the lunches at “chez Traute” and elsewhere, for sharing an office and being there for all the little questions.

Heike Schmidt for her ever cheerful and endlessly patient help with the data collection.

My supervisor, Tania Singer, and all my colleagues at the Max Planck Institute for Human Cognitive and Brain Sciences, in particular Anne Böckler, Nikolaus Steinbeis, Anita Tusche, Veronika Engert and Mathis Trautwein for the constructively critical, joyful and very long discussions and for allowing me to learn a lot.

My family and friends – you made and you make everything possible.

MPI Series in Human Cognitive and Brain Sciences:

1 Anja Hahne
Charakteristika syntaktischer und semantischer Prozesse bei der auditiven Sprachverarbeitung: Evidenz aus ereigniskorrelierten Potentialstudien

2 Ricarda Schubotz
Erinnern kurzer Zeitdauern: Behaviorale und neurophysiologische Korrelate einer Arbeitsgedächtnisfunktion

3 Volker Bosch
Das Halten von Information im Arbeitsgedächtnis: Dissoziationen langsamer corticaler Potentiale

4 Jorge Jovicich
An investigation of the use of Gradient- and Spin-Echo (GRASE) imaging for functional MRI of the human brain

5 Rosemary C. Dymond
Spatial Specificity and Temporal Accuracy in Functional Magnetic Resonance Investigations

6 Stefan Zysset
Eine experimentalpsychologische Studie zu Gedächtnisabrufprozessen unter Verwendung der funktionellen Magnetresonanztomographie

7 Ulrich Hartmann
Ein mechanisches Finite-Elemente-Modell des menschlichen Kopfes

8 Bertram Opitz
Funktionelle Neuroanatomie der Verarbeitung einfacher und komplexer akustischer Reize: Integration haemodynamischer und elektrophysiologischer Maße

9 Gisela Müller-Plath
Formale Modellierung visueller Suchstrategien mit Anwendungen bei der Lokalisation von Hirnfunktionen und in der Diagnostik von Aufmerksamkeitsstörungen

10 Thomas Jacobsen
Characteristics of processing morphological structural and inherent case in language comprehension

11 Stefan Kölsch
Brain and Music
A contribution to the investigation of central auditory processing with a new electrophysiological approach

12 Stefan Frisch
Verb-Argument-Struktur, Kasus und thematische Interpretation beim Sprachverstehen

13 Markus Ullsperger
The role of retrieval inhibition in directed forgetting – an event-related brain potential analysis

14 Martin Koch
Measurement of the Self-Diffusion Tensor of Water in the Human Brain

15 Axel Hutt
Methoden zur Untersuchung der Dynamik raumzeitlicher Signale

16 Frithjof Kruggel
Detektion und Quantifizierung von Hirnaktivität mit der funktionellen Magnetresonanztomographie

17 Anja Dove
Lokalisierung an internen Kontrollprozessen beteiligter Hirngebiete mithilfe des Aufgabenwechselparadigmas und der ereigniskorrelierten funktionellen Magnetresonanztomographie

18 Karsten Steinhauer
Hirnphysiologische Korrelate prosodischer Satzverarbeitung bei gesprochener und geschriebener Sprache

19 Silke Urban
Verbinformationen im Satzverstehen

20 Katja Werheid
Implizites Sequenzlernen bei Morbus Parkinson

21 Doreen Nessler
Is it Memory or Illusion? Electrophysiological Characteristics of True and False Recognition

22 Christoph Herrmann
Die Bedeutung von 40-Hz-Oszillationen für kognitive Prozesse

23 Christian Fiebach
Working Memory and Syntax during Sentence Processing.
A neurocognitive investigation with event-related brain potentials and functional magnetic resonance imaging

24 Grit Hein
Lokalisation von Doppelaufgabendefiziten bei gesunden älteren Personen und neurologischen Patienten

25 Monica de Filippis
Die visuelle Verarbeitung unbeachteter Wörter. Ein elektrophysiologischer Ansatz

26 Ulrich Müller
Die katecholaminerge Modulation präfrontaler kognitiver Funktionen beim Menschen

27 Kristina Uhl
Kontrollfunktion des Arbeitsgedächtnisses über interferierende Information

28 Ina Bornkessel
The Argument Dependency Model: A Neurocognitive Approach to Incremental Interpretation

29 Sonja Lattner
Neurophysiologische Untersuchungen zur auditorischen Verarbeitung von Stimminformationen

30 Christin Grünewald
Die Rolle motorischer Schemata bei der Objektrepräsentation: Untersuchungen mit funktioneller Magnetresonanztomographie

31 Annett Schirmer
Emotional Speech Perception: Electrophysiological Insights into the Processing of Emotional Prosody and Word Valence in Men and Women

32 André J. Szameitat
Die Funktionalität des lateral-präfrontalen Cortex für die Verarbeitung von Doppelaufgaben

33 Susanne Wagner
Verbales Arbeitsgedächtnis und die Verarbeitung ambiger Wörter in Wort- und Satzkontexten

34 Sophie Manthey
Hirn und Handlung: Untersuchung der Handlungsrepräsentation im ventralen prämotorischen Cortex mit Hilfe der funktionellen Magnet-Resonanz-Tomographie

35 Stefan Heim
Towards a Common Neural Network Model of Language Production and Comprehension: fMRI Evidence for the Processing of Phonological and Syntactic Information in Single Words

36 Claudia Friedrich
Prosody and spoken word recognition: Behavioral and ERP correlates

37 Ulrike Lex
Sprachlateralisierung bei Rechts- und Linkshändern mit funktioneller Magnetresonanztomographie

38 Thomas Arnold
Computergestützte Befundung klinischer Elektroenzephalogramme

39 Carsten H. Wolters
Influence of Tissue Conductivity Inhomogeneity and Anisotropy on EEG/MEG based Source Localization in the Human Brain

40 Ansgar Hantsch
Fisch oder Karpfen? Lexikale Aktivierung von Benennungsalternative bei der Objektbenennung

41 Peggy Bungert
Zentralnervöse Verarbeitung akustischer Informationen Signalidentifikation, Signallateralisation und zeitgebundene Informationsverarbeitung bei Patienten mit erworbenen Hirnschädigungen

42 Daniel Senkowski
Neuronal correlates of selective attention: An investigation of electrophysiological brain responses in the EEG and MEG

43 Gert Wollny
Analysis of Changes in Temporal Series of Medical Images

44 Angelika Wolf
Sprachverstehen mit Cochlea-Implantat: EKP-Studien mit postlingual ertaubten erwachsenen CI-Trägern

45 Kirsten G. Volz
Brain correlates of uncertain decisions: Types and degrees of uncertainty

46 Hagen Huttner
Magnetresonanztomographische Untersuchungen über die anatomische Variabilität des Frontallappens des menschlichen Großhirns

47 Dirk Köster
Morphology and Spoken Word Comprehension: Electrophysiological Investigations of Internal Compound Structure

48 Claudia A. Hruska
Einflüsse kontextueller und prosodischer Informationen in der auditorischen Satzverarbeitung: Untersuchungen mit ereigniskorrelierten Hirnpotentialen

49 Hannes Ruge
Eine Analyse des raum-zeitlichen Musters neuronaler Aktivierung im Aufgabenwechselparadigma zur Untersuchung handlungssteuernder Prozesse

50 Ricarda I. Schubotz
Human premotor cortex: Beyond motor performance

51 Clemens von Zerssen
Bewusstes Erinnern und falsches Wiedererkennen: Eine funktionelle MRT Studie neuroanatomischer Gedächtniskorrelate

52 Christiane Weber
Rhythm is gonna get you.
Electrophysiological markers of rhythmic processing in infants with and without risk for Specific Language Impairment (SLI)

53 Marc Schönwiesner
Functional Mapping of Basic Acoustic Parameters in the Human Central Auditory System

54 Katja Fiehler
Temporospatial characteristics of error correction

55 Britta Stolterfoht
Processing Word Order Variations and Ellipses: The Interplay of Syntax and Information Structure during Sentence Comprehension

56 Claudia Danielmeier
Neuronale Grundlagen der Interferenz zwischen Handlung und visueller Wahrnehmung

57 Margret Hund-Georgiadis
Die Organisation von Sprache und ihre Reorganisation bei ausgewählten, neurologischen Erkrankungen gemessen mit funktioneller Magnetresonanztomographie – Einflüsse von Händigkeit, Läsion, Performanz und Perfusion

58 Jutta L. Mueller
Mechanisms of auditory sentence comprehension in first and second language: An electrophysiological miniature grammar study

59 Franziska Biedermann
Auditorische Diskriminationsleistungen nach unilateralen Läsionen im Di- und Telenzephalon

60 Shirley-Ann Rüschemeyer
The Processing of Lexical Semantic and Syntactic Information in Spoken Sentences: Neuroimaging and Behavioral Studies of Native and Non-Native Speakers

61 Kerstin Leuckefeld
The Development of Argument Processing Mechanisms in German. An Electrophysiological Investigation with School-Aged Children and Adults

62 Axel Christian Kühn
Bestimmung der Lateralisierung von Sprachprozessen unter besondere Berücksichtigung des temporalen Cortex, gemessen mit fMRT

63 Ann Pannekamp
Prosodische Informationsverarbeitung bei normalsprachlichem und deviantem Satzmaterial: Untersuchungen mit ereigniskorrelierten Hirnpotentialen

64 Jan Derrfuß
Functional specialization in the lateral frontal cortex: The role of the inferior frontal junction in cognitive control

65 Andrea Mona Philipp
The cognitive representation of tasks – Exploring the role of response modalities using the task-switching paradigm

66 Ulrike Toepel
Contrastive Topic and Focus Information in Discourse – Prosodic Realisation and Electrophysiological Brain Correlates

67 Karsten Müller
Die Anwendung von Spektral- und Waveletanalyse zur Untersuchung der Dynamik von BOLD-Zeitreihen verschiedener Hirnareale

68 Sonja A.Kotz
The role of the basal ganglia in auditory language processing: Evidence from ERP lesion studies and functional neuroimaging

69 Sonja Rossi
The role of proficiency in syntactic second language processing: Evidence from event-related brain potentials in German and Italian

70 Birte U. Forstmann
Behavioral and neural correlates of endogenous control processes in task switching

71 Silke Paulmann
Electrophysiological Evidence on the Processing of Emotional Prosody: Insights from Healthy and Patient Populations

72 Matthias L. Schroeter
Enlightening the Brain – Optical Imaging in Cognitive Neuroscience

73 Julia Reinholz
Interhemispheric interaction in object- and word-related visual areas

74 Evelyn C. Ferstl
The Functional Neuroanatomy of Text Comprehension

75 Miriam Gade
Aufgabeninhibition als Mechanismus der Konfliktreduktion zwischen Aufgabenrepräsentationen

76 Juliane Hofmann
Phonological, Morphological, and Semantic Aspects of Grammatical Gender Processing in German

77 Petra Augurzky
Attaching Relative Clauses in German – The Role of Implicit and Explicit Prosody in Sentence Processing

78 Uta Wolfensteller
Habituelle und arbiträre sensomotorische Verknüpfungen im lateralen prämotorischen Kortex des Menschen

79 Päivi Sivonen
Event-related brain activation in speech perception: From sensory to cognitive processes

80 Yun Nan
Music phrase structure perception: the neural basis, the effects of acculturation and musical training

81 Katrin Schulze
Neural Correlates of Working Memory for Verbal and Tonal Stimuli in Nonmusicians and Musicians With and Without Absolute Pitch

82 Korinna Eckstein
Interaktion von Syntax und Prosodie beim Sprachverstehen: Untersuchungen anhand ereigniskorrelierter Hirnpotentiale

83 Florian Th. Siebörger
Funktionelle Neuroanatomie des Textverstehens: Kohärenzbildung bei Witzen und anderen ungewöhnlichen Texten

84 Diana Böttger
Aktivität im Gamma-Frequenzbereich des EEG: Einfluss demographischer Faktoren und kognitiver Korrelate

85 Jörg Bahlmann
Neural correlates of the processing of linear and hierarchical artificial grammar rules: Electrophysiological and neuroimaging studies

86 Jan Zwickel
Specific Interference Effects Between Temporally Overlapping Action and Perception

87 Markus Ullsperger
Functional Neuroanatomy of Performance Monitoring: fMRI, ERP, and Patient Studies

88 Susanne Dietrich
Vom Brüllen zum Wort – MRT-Studien zur kognitiven Verarbeitung emotionaler Vokalisationen

89 Maren Schmidt-Kassow
What's Beat got to do with ist? The Influence of Meter on Syntactic Processing: ERP Evidence from Healthy and Patient populations

90 Monika Lück
Die Verarbeitung morphologisch komplexer Wörter bei Kindern im Schulalter: Neurophysiologische Korrelate der Entwicklung

91 Diana P. Szameitat
Perzeption und akustische Eigenschaften von Emotionen in menschlichem Lachen

92 Beate Sabisch
Mechanisms of auditory sentence comprehension in children with specific language impairment and children with developmental dyslexia: A neurophysiological investigation

93 Regine Oberecker
Grammatikverarbeitung im Kindesalter: EKP-Studien zum auditorischen Satzverstehen

94 Şükrü Barış Demiral
Incremental Argument Interpretation in Turkish Sentence Comprehension

95 Henning Holle
The Comprehension of Co-Speech Iconic Gestures: Behavioral, Electrophysiological and Neuroimaging Studies

96 Marcel Braß
Das inferior frontale Kreuzungsareal und seine Rolle bei der kognitiven Kontrolle unseres Verhaltens

97 Anna S. Hasting
Syntax in a blink: Early and automatic processing of syntactic rules as revealed by event-related brain potentials

98 Sebastian Jentschke
Neural Correlates of Processing Syntax in Music and Language – Influences of Development, Musical Training and Language Impairment

99 Amelie Mahlstedt
The Acquisition of Case marking Information as a Cue to Argument Interpretation in German
An Electrophysiological Investigation with Pre-school Children

100 Nikolaus Steinbeis
Investigating the meaning of music using EEG and fMRI

101 Tilmann A. Klein
Learning from errors: Genetic evidence for a central role of dopamine in human performance monitoring

102 Franziska Maria Korb
Die funktionelle Spezialisierung des lateralen präfrontalen Cortex: Untersuchungen mittels funktioneller Magnetresonanztomographie

103 Sonja Fleischhauer
Neuronale Verarbeitung emotionaler Prosodie und Syntax: die Rolle des verbalen Arbeitsgedächtnisses

104 Friederike Sophie Haupt
The component mapping problem: An investigation of grammatical function reanalysis in differing experimental contexts using eventrelated brain potentials

105 Jens Brauer
Functional development and structural maturation in the brain's neural network underlying language comprehension

106 Philipp Kanske
Exploring executive attention in emotion: ERP and fMRI evidence

107 Julia Grieser Painter
Music, meaning, and a semantic space for musical sounds

108 Daniela Sammler
The Neuroanatomical Overlap of Syntax Processing in Music and Language - Evidence from Lesion and Intracranial ERP Studies

109 Norbert Zmyj
Selective Imitation in One-Year-Olds: How a Model's Characteristics Influence Imitation

110 Thomas Fritz
Emotion investigated with music of variable valence – neurophysiology and cultural influence

111 Stefanie Regel
The comprehension of figurative language: Electrophysiological evidence on the processing of irony

112 Miriam Beisert
Transformation Rules in Tool Use

113 Veronika Krieghoff
Neural correlates of Intentional Actions

114 Andreja Bubić
Violation of expectations in sequence processing

115 Claudia Männel
Prosodic processing during language acquisition: Electrophysiological studies on intonational phrase processing

116 Konstanze Albrecht
Brain correlates of cognitive processes underlying intertemporal choice for self and other

117 Katrin Sakreida
Nicht-motorische Funktionen des prämotorischen Kortex: Patientenstudien und funktionelle Bildgebung

118 Susann Wolff
The interplay of free word order and pro-drop in incremental sentence processing: Neurophysiological evidence from Japanese

119 Tim Raettig
The Cortical Infrastructure of Language Processing: Evidence from Functional and Anatomical Neuroimaging

120 Maria Golde
Premotor cortex contributions to abstract and action-related relational processing

121 Daniel S. Margulies
Resting-State Functional Connectivity fMRI: A new approach for assessing functional neuroanatomy in humans with applications to neuroanatomical, developmental and clinical questions

122 Franziska Süß
The interplay between attention and syntactic processes in the adult and developing brain: ERP evidences

123 Stefan Bode
From stimuli to motor responses: Decoding rules and decision mechanisms in the human brain

124 Christiane Diefenbach
Interactions between sentence comprehension and concurrent action: The role of movement effects and timing

125 Moritz M. Daum
Mechanismen der frühkindlichen Entwicklung des Handlungsverständnisses

126 Jürgen Dukart
Contribution of FDG-PET and MRI to improve Understanding, Detection and Differentiation of Dementia

127 Kamal Kumar Choudhary
Incremental Argument Interpretation in a Split Ergative Language: Neurophysiological Evidence from Hindi

128 Peggy Sparenberg
Filling the Gap: Temporal and Motor Aspects of the Mental Simulation of Occluded Actions

129 Luming Wang
The Influence of Animacy and Context on Word Order Processing: Neurophysiological Evidence from Mandarin Chinese

130 Barbara Ettrich
Beeinträchtigung frontomedianer Funktionen bei Schädel-Hirn-Trauma

131 Sandra Dietrich
Coordination of Unimanual Continuous Movements with External Events

132 R. Muralikrishnan
An Electrophysiological Investigation Of Tamil Dative-Subject Constructions

133 Christian Obermeier
Exploring the significance of task, timing and background noise on gesture-speech integration

134 Björn Herrmann
Grammar and perception: Dissociation of early auditory processes in the brain

135 Eugenia Solano-Castiella
In vivo anatomical segmentation of the human amygdala and parcellation of emotional processing

136 Marco Taubert
Plastizität im sensomotorischen System – Lerninduzierte Veränderungen in der Struktur und Funktion des menschlichen Gehirns

137 Patricia Garrido Vásquez
Emotion Processing in Parkinson's Disease: The Role of Motor Symptom Asymmetry

138 Michael Schwartze
Adaptation to temporal structure

139 Christine S. Schipke
Processing Mechanisms of Argument Structure and Case-marking in Child Development: Neural Correlates and Behavioral Evidence

140 Sarah Jessen
Emotion Perception in the Multisensory Brain

141 Jane Neumann
Beyond activation detection: Advancing computational techniques for the analysis of functional MRI data

142 Franziska Knolle
Knowing what's next: The role of the cerebellum in generating predictions

143 Michael Skeide
Syntax and semantics networks in the developing brain

144 Sarah M. E. Gierhan
Brain networks for language
Anatomy and functional roles of neural pathways supporting language comprehension and repetition

145 Lars Meyer
The Working Memory of Argument-Verb Dependencies
Spatiotemporal Brain Dynamics during Sentence Processing

146 Benjamin Stahl
Treatment of Non-Fluent Aphasia through Melody, Rhythm and Formulaic Language

147 Kathrin Rothermich
The rhythm's gonna get you: ERP and fMRI evidence on the interaction of metric and semantic processing

148 Julia Merrill
Song and Speech Perception – Evidence from fMRI, Lesion Studies and Musical Disorder

149 Klaus-Martin Krönke
Learning by Doing?
Gesture-Based Word-Learning and its Neural Correlates in Healthy Volunteers and Patients with Residual Aphasia

150 Lisa Joana Knoll
When the hedgehog kisses the frog
A functional and structural investigation of syntactic processing in the developing brain

151 Nadine Diersch
Action prediction in the aging mind

152 Thomas Dolk
A Referential Coding Account for the Social Simon Effect

153 Mareike Bacha-Trams
Neurotransmitter receptor distribution in Broca's area and the posterior superior temporal gyrus

154 Andrea Michaela Walter
The role of goal representations in action control

155 Anne Keitel
Action perception in development: The role of experience

156 Iris Nikola Knierim
Rules don't come easy: Investigating feedback-based learning of phonotactic rules in language.

157 Jan Schreiber
Plausibility Tracking: A method to evaluate anatomical connectivity and microstructural properties along fiber pathways

158 Katja Macher
Die Beteiligung des Cerebellums am verbalen Arbeitsgedächtnis

159 Julia Erb
The neural dynamics of perceptual adaptation to degraded speech