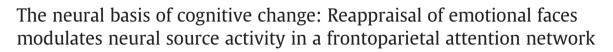
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ABSTRACT

Emotions can be regulated effectively via cognitive change, as evidenced by cognitive behavioural therapy. The neural correlates of cognitive change were investigated using reappraisal, a strategy that involves the reinterpretation of emotional stimuli. Hemodynamic studies revealed cortical structures involved in reappraisal and highlighted the role of the prefrontal cortex in regulating subcortical affective processing. Studies using event-related potentials elucidated the timing of reappraisal by showing effective modulation of the Late Positive Potential (LPP) after 300 ms but also even earlier effects. The present study investigated the spatiotemporal dynamics of the cortical network underlying cognitive change via inverse source modelling based on whole-head magnetoencephalography (MEG). During MEG recording, 28 healthy participants saw angry and neutral faces and followed instructions designed to down- or up-regulate emotions via reappraisal. Differences between angry and neutral face processing were specifically enhanced during up-regulation, first in the parietal cortex during M170 and across the whole cortex during LPP-M, with particular involvement of the parietal and dorsal prefrontal cortex regions. Thus, our data suggest that the reappraisal of emotional faces involves specific modulations in a frontoparietal attention network.

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Introduction

"There is nothing either good or bad, but thinking makes it so." What this famous dictum of Shakespeare's Hamlet suggests is that the way we think changes the way we feel. The idea that cognitive processes influence emotional states is a foundation of cognitive behavioural approaches to the aetiology of mental disorders. Patients with anxiety disorders or major depression, for instance, show a cognitive bias for threatening or negative information, which is believed to promote negative emotions (Beck, 1976; Gibb et al., 2004; Ouimet et al., 2009). Consequently, in cognitive behavioural therapy, the regulation of negative emotions may be restored by interventions that cognitively change these biases, and considerable evidence shows this approach to be successful (Hallion and Ruscio, 2011; Jacobsen et al., 2011; Ougrin, 2011). Therefore, cognitive change as a mechanism underlying emotion regulation is of great relevance to the aetiology, treatment and prevention of mental disorders. Accordingly, a deeper understanding of this mechanism and its neural basis is of great interest and will be the focus of this study.

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A technique frequently used to study cognitive change in experimental designs is reappraisal, a strategy that involves the reinterpretation of a situation or stimulus in a way that changes its emotional impact (e.g., Gross and John, 2003). In a number of reappraisal experiments, participants are instructed to down-regulate their upcoming emotional response to unpleasant scenes by taking a third-person perspective or imagining a positive outcome of the depicted scene. Conversely, up-regulation of emotions to the same stimuli can be accomplished by instructions to take a first-person perspective or to imagine a negative outcome of the scene (e.g., Ochsner et al., 2004). Effects of reappraisal are usually assessed as changes during a down- or an up-regulation condition compared to a passive viewing condition. In the same vein, many studies have demonstrated the effectiveness of reappraisal in regulating emotion on experiential, behavioural, physiological and neural levels (Gross, 2002; Ochsner and Gross, 2005, 2008; Ray et al., 2010; Urry, 2009).

Studies using functional magnetic resonance imaging (fMRI) revealed evidence of the neural structures involved in reappraisal. For both up- and down-regulation via reappraisal, enhanced neural activity was observed in regions associated with cognitive control, such as the prefrontal and cingulate cortices. However, regions known to be involved in emotion generation, such as the amygdala and insula, revealed enhanced neural activity during up-regulation and attenuated neural activity during down-regulation. These findings were integrated in a neural model of cognitive emotion regulation, in which cognitive



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strategies rely on specific component control processes, such as attention, language, and working memory. These are mediated by the prefrontal and cingulate cortices, which exert regulatory effects on emotion-generating systems, such as the amygdala and insula (see Ochsner and Gross, 2005, 2008 for reviews).

Studies using Event Related Potentials (ERPs) have provided information regarding the time course of reappraisal. Most of these studies focused on a parietal positivity that occurs after 300 ms, called the Late Positive Potential (LPP). The LPP is the latest and most robust of several visual ERP components, which are known to be enhanced by emotional compared to neutral stimulus content (see Schupp et al., 2006; Olofsson et al., 2008 for reviews). This stimulus-driven enhancement of amplitude may be termed *emotion effect* and is believed to reflect motivated attention to stimuli of potentially vital importance. According to a neural model of motivated attention, the emotion effect is mediated by enhanced activity in visual processing areas in the occipital, parietal and temporal cortices, which is evoked via re-entrant projections from emotion-generating systems, such as the amygdala (Lang and Bradley, 2010).

It follows that, much like variability in the amygdala, the LPP can be studied as a neural marker of emotional processing. Accordingly, several ERP studies have shown that LPP amplitudes can be modulated by reappraisal just as by emotion, most likely reflecting variations in subjective emotional intensity. Instructions to down-regulate emotional responses via reappraisal reduced LPP amplitudes compared to passively viewed emotional pictures (Hajcak and Nieuwenhuis, 2006; Krompinger et al., 2008; Moser et al., 2006, 2009, 2010; Thiruchselvam et al., 2011), whereas instructions to up-regulate emotional responses further enhanced LPP amplitudes (Moser et al., 2009, 2010). Regarding the relative onset of emotion and reappraisal effects, emotional modulations were reported to start earlier (around 150 ms; Olofsson et al., 2008) than modulations by reappraisal (around 300 ms) across different studies. When investigated within the same study, such a successive start was shown in some (Krompinger et al., 2008; Moser et al., 2009; Thiruchselvam et al., 2011), but not all cases (Hajcak and Nieuwenhuis, 2006; Moser et al., 2006, but note that early emotion effects were not analysed). However, as these ERP studies analysed LPP amplitudes in one single or few parietal central electrodes, conclusions regarding the underlying neural network could not be drawn directly from these data.

In a recently established altered experimental set-up, reappraisal was implemented by predefined negative or neutral verbal descriptions of upcoming emotional scenes (Foti and Hajcak, 2008; MacNamara et al., 2009, 2011), an approach that was labelled *preappraisal* (Hajcak et al. (in press). Modulations of LPP amplitudes using this design replicated previous findings: unpleasant pictures, which were preceded by negative descriptions, elicited greater LPP amplitudes than unpleasant pictures preceded by neutral descriptions. Moreover, this implementation of reappraisal prior to picture presentation revealed the so far earliest effect of reappraisal between 50 and 150 ms at posterior sites. This was followed by an emotion effect between 150 and 250 ms at anterior sites that was insensitive to reappraisal (Foti and Hajcak, 2008). Reappraisal effects in the LPP were reported in all studies using preappraisal, and a more fine-grained spatial analysis showed spatiotemporally distinct portions of the LPP to be modulated either by reappraisal, by emotion, or the combination of both (Foti and Hajcak, 2008; MacNamara et al., 2009, 2011). In addition, a reduced LPP at parietal electrodes during down-regulation by reappraisal was recently shown to be accompanied by reduced alpha power at left frontal electrodes, presumably reflecting enhanced left prefrontal activity (Parvaz et al., 2012). Taken together, these dissociations regarding time course as well as topography and spectral power suggest that stimulus-driven emotion and cognitively driven reappraisal may constitute - at least in part - different processes, possibly mediated by different neural generators across time.

As yet, there are not any source localisations available which could ascribe the observed electrophysiological modulations by reappraisal to its underlying neural generators. For this purpose, source reconstruction which is based on whole-head high-density magnetoencephalography (MEG) and which can, thus, resort to a large number of sensors and excellent coverage, is particularly suitable to enable the assignment of time-dependent effects to larger cortical structures. Against this background, the aim of the present study was to elucidate the time course of estimated neural source activity associated with stimulus-driven emotional perception and cognitively driven reappraisal. To this end, MEG was recorded while 28 healthy participants saw pictures of angry or neutral facial expressions. Prior to the picture presentation, participants were given reappraisal instructions involving the imagination of the depicted persons in different social situations. In the case of up-regulation (ThreatUp), participants were instructed to imagine a threatening situation in which they are confronted with an angry opponent. In the case of down-regulation (ThreatDown), participants were instructed to imagine a safe situation in which they were asked to evaluate the performance of an actor. In a third control condition, participants were instructed to relax and attentively view the pictures (View). To further determine the effectiveness of reappraisal on cognitive threat appraisal and peripheral emotional arousal, subjective threat ratings of the presented faces were obtained and electrodermal activity (EDA) was recorded.

This design deviates from previous reappraisal paradigms with respect to the use of facial stimuli and the implementation of reappraisal, which limits its comparability, but also provides several major advantages:

First, emotional facial expressions seem quite suitable for the study of reappraisal, since fMRI studies already evidenced effective modulations of neural face processing by reappraisal (Kompus et al., 2009; Kim et al., 2004). Even more importantly, ERP studies showed that the N170, a face-specific occipito-temporal negativity occurring around 170 ms, is enhanced in response to negative (vs. neutral) facial expressions when faces are presented in a congruent pictorial emotional context (Frühholz et al., 2009; Righart and de Gelder, 2006, 2008) or while participants are in an anxious state (Wieser et al., 2010). This sensitivity to emotional context suggests that the N170 might also be susceptible to short-latency effects of reappraisal. In addition, especially short latency ERPs, like the N170 or EPN, are modulated by systematic differences in stimulus complexity (Bradley et al., 2007; Rossion and Jacques, 2008). Hence, the reduced degree of physical and semantic variance of emotional faces compared to more complex emotional scenes may enable an improved assessment of reappraisal effects on short-latency components.

Second, the present design allows for a direct comparison of emotion and regulation conditions under most equal circumstances. So far, many studies excluded neutral stimuli from regulation conditions, trying to avoid potential confusion of participants, but at the same time accepting the restricted comparability of passively viewed neutral with regulated emotional stimuli. In contrast to the frequently used emotional scenes, which are usually taken from a variety of picture categories (people, animals, mutilations, landscapes, etc.), facial expressions reflect a single category with different affective gradations. In the present reappraisal conditions, though, neutral faces may well be interpreted as less expressive or less angry without leading to confusion. As a result, the influence of reappraisal on the emotion effect can be captured directly within the same experimental condition, avoiding confounding variables such as different task demands. In a similar way, two opposite reappraisal conditions (ThreatDown and ThreatUp) can be directly contrasted against each other. With the exception of the direction of regulation, both conditions were designed to be comparable with regard to cognitive load, need for imagination or inner speech, and direction of attention towards emotional aspects of the stimuli. The instructions were also standardised, applied before stimulus onset, and did not comprise any explicit demand to manipulate emotional responses, which is consistent with advances of previous studies (Foti and Hajcak, 2008; MacNamara et al., 2009, 2011). The close matching of the two conditions clearly enhances the

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