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RESEARCH ARTICLE

REVISED Anterior and posterior subareas of the dorsolateral frontal cortex in socially relevant decisions based on masked affect expressions [v3; ref status: indexed, http://f1000r.es/5ke]

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Abstract
Socially-relevant decisions are based on clearly recognizable but also not consciously accessible affective stimuli. We studied the role of the dorsolateral frontal cortex (DLFC) in decision-making on masked affect expressions using functional magnetic resonance imaging. Our paradigm permitted us to capture brain activity during a pre-decision phase when the subjects viewed emotional expressions below the threshold of subjective awareness, and during the decision phase, which was based on verbal descriptions as the choice criterion. Using meta-analytic connectivity modeling, we found that the preparatory phase of the decision was associated with activity in a right-posterior portion of the DLFC featuring co-activations in the left-inferior frontal cortex. During the subsequent decision a right-anterior and more dorsal portion of the DLFC became activated, exhibiting a different co-activation pattern. These results provide evidence for partially independent sub-regions within the DLFC, supporting the notion of dual associative processes in intuitive judgments.

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REVISED version 3 published 09 Jul 2015	✓	✓ report
REVISED version 2 published 20 Apr 2015	? report	? report
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Competing interests: No competing interests were disclosed.

Introduction

Reading of, and reacting to the numerous dynamic and variable nonverbal signals that are sent out voluntarily or unintentionally in an everyday social situation is challenging and requires the interaction of many brain systems (Frith & Frith, 2003; Xi *et al.*, 2011). Particularly in social situations, people tend to evaluate their surroundings, including their interaction partner (Ellsworth & Scherer, 2003). The human face is the most important object for such an evaluation, since it acts as a key component in conveying socially relevant messages in rapid succession (Ekman & Friesen, 1969). Owing to the complexity of social encounters and the many communicative signals produced by rapidly changing facial expressions, it appears likely that some facial expressions might be too subtle to be perceived fully consciously by the addressee. However, even these transient signals might be of high relevance in "gut-feeling"-based social decisions. For example, inferring even a slightly aggressive emotional state from another's behavior or facial expression might be crucial for the decision between appeasement in order to avoid confrontation or provocation. Thereby, understanding the mental state of others can be self-profitable for the individual.

The affective primacy hypothesis (Murphy & Zajonc, 1993) highlights the effects of not consciously perceived affective information, stating that affect can be elicited prior to cognitive processing even when its origin is not consciously accessible. In line with this assumption, studies have shown that subliminal stimuli are processed similarly to consciously accessible stimuli (Henson *et al.*, 2008; Nomura *et al.*, 2004; Prochnow *et al.*, 2013b). Hence they are able to affect attitudes and judgments which are potent determinants of decision-making in complex situations (Dimberg *et al.*, 2000; Li *et al.*, 2008; Moskowitz *et al.*, 2012; Ruys & Aarts, 2012; Sweeny *et al.*, 2009; Winkielman *et al.*, 2005).

Decision-making as a term subsumes multiple aspects such as different phases as well as the circumstances of decision-making, such as risky decisions and ambiguous decisions (Bechara *et al.*, 2005). Typically, gambling paradigms are used to study decision-making (Bechara *et al.*, 1994; Bechara *et al.*, 2005; Brand *et al.*, 2005; Brand *et al.*, 2006). However, there exist also standardized

paradigms with more emphasis on social aspects like the Ultimatum Game or the Prisoner's Dilemma Game (Baumgartner *et al.*, 2011; Güth *et al.*, 1982; Sanfey, 2007; van't Wout *et al.*, 2005). Due to the omnipresence of decisions in everyday life, many different experimental settings are suited to assess socially relevant decisions and decision-making often appears to be implicitly studied in mental state reasoning or theory of mind (ToM) paradigms (Hall *et al.*, 2010; Hooker *et al.*, 2008; Mériau *et al.*, 2006; Prochnow *et al.*, 2013a; Reniers *et al.*, 2012; Walter *et al.*, 2004). Recent evidence, however, suggests that gambling and ToM scenarios are based at least partly on different neural circuits (Xi *et al.*, 2011).

Svenson's "Differentiation and Consolidation Theory" (1996) considers decision-making as the result of a number of different sub-processes. These comprise a pre-decision phase during which different choice alternatives are compared, the decision itself and a post-decision consolidation phase. Following the theory, a number of studies investigated the preparatory processes of different kinds of real-life and gambling decisions and found that the ventromedial frontal cortex (VMFC) and dorsolateral frontal cortex (DLFC) are related to the computation of decision values (Camus *et al.*, 2009; Hall *et al.*, 2010; Jocham *et al.*, 2012; Litt *et al.*, 2011; Reniers *et al.*, 2012; Sokol-Hessner *et al.*, 2012; van't Wout *et al.*, 2005). Further evidence suggests that both regions continuously share information during this process (Baumgartner *et al.*, 2011; Sokol-Hessner *et al.*, 2012), along with other interconnected areas within the prefrontal cortex (Miller & Cohen, 2001). The DLFC has also been identified as crucially involved in decisions involving ambiguity or uncertainty, paradigms which are considered being predominantly cognitive in nature (Hosseini *et al.*, 2010; Krain *et al.*, 2006). Accordingly, the DLFC has traditionally been linked to cognitive control and monitoring processes (Cole & Schneider, 2007; Durston *et al.*, 2003; Milham *et al.*, 2003; Wagner *et al.*, 2001).

However, increasing evidence shows, that DLFC engagement is not limited to decision and judgment tasks in a predominantly cognitive environment but is found in social and affective contexts as well (Bzdok *et al.*, 2012a; Hall *et al.*, 2010; Lawrence *et al.*, 2006; Opialla *et al.*, 2015; Prochnow *et al.*, 2013a; Prochnow *et al.*, 2013b; Prochnow *et al.*, 2014b; Silvers *et al.*, 2015; Thirioux *et al.*, 2014; Walter *et al.*, 2004). Anatomically, the DLFC has close connections to the parietal and premotor cortices, via the thalamus to the cerebellum (Hoshi, 2006) and also to regions that have been critically implicated in mentalizing, such as the temporo-parietal junction (Bzdok *et al.*, 2012b; Kucyi *et al.*, 2012), the anterior cingulate cortex (ACC), and right-inferior frontal gyrus (IFG) (Cieslik *et al.*, 2013). Notably, in line with previous research highlighting the important role of the DLFC in the preparatory stages of a decision, we found DLFC activity when subjects were presented with either subtle or prominent emotional expressions on which a subsequent decision should be based (Prochnow *et al.*, 2013b; Prochnow *et al.*, 2014b). Conversely, the DLFC became also engaged late during the actual discrimination and categorization of evolving emotional facial expressions, even when the executive load was partly controlled (Prochnow *et al.*, 2013a). While in our studies the activation tended to be located in posterior parts of the DLFC during preparation of the decision, it was located more anterior when the decision itself took place.

In the current functional magnetic resonance imaging (fMRI) study we extended the earlier study (Prochnow *et al.*, 2013b) to investigate the role of the dorsolateral frontal cortex (DLFC) in socially relevant decisions based on subtle emotional information. In the light of our previous results implicating the DLFC both in the preparatory stage of decision-making as well as in the actual decision, our novel paradigm permitted differentiating between both sub-processes within the same decision process. In particular, we presented facial expressions showing very short (40 ms) happy, angry or sad expressions, which were immediately superimposed by a neutral expression of the same actor, which masked the subtle emotional expression the participants had to evaluate. In this preparatory stage of the decision process, the subjects were already aware that a decision had to be made on the basis of the ambiguous facial expression but necessary information to actually make the decision was still lacking. The actual decision could not been made until pairs of emotional adjectives serving as the decision criterion were presented along with the instruction to decide which adjective matched best the previously seen facial expression. This approach permitted us to explore the role of the DLFC in relation to different aspects of socially-relevant decisions.

We hypothesized that the DLFC becomes active when socially relevant decisions based on subtle emotional information which is not accessible to fully conscious perception are made. Specifically, based on our own previous data, as well as evidence from primate studies and network analyses (cf. Hoshi, 2006 for a review; Cieslik *et al.*, 2013), we predicted that the pre-decision phase and subsequent decision engage different subareas within the DLFC, and that this at least partly functional specialization is reflected by different co-activation patterns.

Materials and methods

The paradigm used in this study and described in detail in the following section has been previously used in another study comparing brain activation patterns between facial expressions of emotion which were either clearly visible or presented below the threshold of subjective awareness (Prochnow *et al.*, 2013b). It has been designed in order to being able to test different hypotheses related to the processing of subliminal information based on the same paradigm. Other than the previous study, the current work focuses on the decision aspect of the overall paradigm since the subjects were instructed to decide which of two subsequently presented emotional adjectives best described the mood observed in the previously seen face. Furthermore, this paper addresses the novel issue of functional connectivity of the activated lateral prefrontal cortex.

Participants

The screening of the participants comprised of assessments of handedness (Edinburgh inventory, Oldfield, 1971), alexithymia (TAS-20, Bagby *et al.*, 1994), depressiveness (BDI, Hautzinger *et al.*, 1994), empathy (SPF, German adaptation of the Interpersonal Reactivity Index, http://psydok.sulb.uni-saarland.de/volltexte/2009/2363/pdf/SPF_Artikel.pdf) and affect (PANAS, Watson *et al.*, 1988) in order to only enroll participants with an intact ability to understand emotions and infer emotional states. Exclusion criteria were: left handedness, signs of alexithymia (TAS-20 > 52) or depressiveness (BDI > 9), low self-reported empathy (SPF scale fantasy < 10, SPF

scale perspective-taking < 13, SPF scale empathic concern < 12), critical life events during the last year (assessed by means of a short self-developed questionnaire asking whether the participants recently experienced the loss of a beloved one or other traumata), a predominantly negative mood on the day of testing (PANAS negative affect > positive affect), intake of psychotropic drugs or a contraindication of fMRI scanning. Contraindications could be pregnancy, fMRI incompatible or irremovable metals like pacemakers or implants, claustrophobia, and fraction anomalies of sight that could not be corrected by MRI suitable glasses or contact lenses. Participants were recruited using flyers on the university campus. From the 18 participants fulfilling the inclusion criteria for the fMRI study, six were later excluded from data analysis due to movement artifacts or reports of being aware of the subtle emotional expressions indicating a too low threshold of subjective awareness which would have been a confounding factor (see the next section for more information on the debriefing procedure). All participants had normal or corrected-to-normal vision and gave informed written consent to participate in the fMRI study and for publication of the study results. Experiments were approved by the ethics committee of the Heinrich-Heine University Düsseldorf (project # 3614) and conducted according to the Declaration of Helsinki. Statistical data analysis was performed on the data from the remaining 12 healthy volunteers (5 men/7 women) who had a mean age of 23.8 (SD = 3.0) and a median of 16.5 (9–18) years of education.

Stimulus material and stimulation procedure

During fMRI scanning, participants lay supine in the scanner and viewed the experimental stimuli through a mirror attached to the head coil. The images were presented using presentation software (Version 14.9, Neurobehavioral Systems Inc., Albany CA). During stimulation, participants were presented with male and female facial expressions of emotion depicting happiness, anger or sadness via projection on a semitransparent screen installed in the scanner room using an LCD-projector positioned outside the scanner room (Ekman & Friesen Picture Set, Ekman & Friesen, 1976). Presented were just the faces, while the remaining parts of the heads including the hair and ears were concealed by the blank of the background. The faces were followed by a blank of 2600 ms on average which was jittered randomly between 400 and 4800 ms. Thereafter, pairs of emotional adjectives were presented as text on screen for 3000 ms (e.g. sorrowful (betrübt) – annoyed (verärgert)) after a jittered (400–4800 ms) time interval. They were instructed to imagine being confronted with someone showing the particular facial expression and to press one of two response buttons (left, right) to decide which adjective corresponded best to the affect of the person depicted. If they felt that none of the adjectives would match, they were requested to choose the best fit (forced choice paradigm).

In 96 experimental trials which were scanned consecutively in one scanning session, the facial expressions of emotion were shown for only 40 ms and then superimposed by a masking neutral expression of the same person for 360 ms. Each emotion (happy, angry, sad) was repeated 32 times in a pseudorandomized order. In addition, there were another 96 trials in which no masking technique was applied and the emotional expression lasted for 400 ms (for a comparison of the masked emotional and unmasked emotional conditions, see Prochnow *et al.*, 2013b) Also, we used

scrambled versions of the face images to measure baseline as typically used to map the cerebral areas specifically related to face perception (Slotnik & White, 2013; Zhu *et al.*, 2013). These scrambled images were produced from the digitized images of the faces used and corrected for luminescence. Thus, the scrambled images had the same visual features as the images of the faces and were presented in an identical manner as the faces. Specifically, the scrambled images of the emotional faces were presented for 400ms in the unmasked condition, while the scrambled images of the emotional faces were presented for 40ms followed by presentation of the scrambled images of the neural faces for 360 ms in the masked condition. Accordingly, the scrambled images were alterations of the original image maintaining the basic visual features but removing meaning from the image.

Masking is a common technique validated by many studies suited to prevent a short stimulus from being consciously perceived (e.g. Dimberg *et al.*, 2000; Suslow *et al.*, 2013). In order to ensure that despite of the masking technique, our subjects were not aware of the masked emotional expression, they were subjected to a post scanning debriefing similar to the one described in Chartrand & Bargh (1996). The debriefing consisted of increasingly precise questions about the assumed goal of the study, the perception of the stimuli and the procedure. Most participants thought the study was about decision-making or subjective judgments of different facial expressions. However, eight participants (26%) had a suspicion that there were emotional faces presented very shortly before the neutral faces. These were excluded from further data analysis. Furthermore, 78% reported to have noticed a flickering in some of the trials, but did not attribute any meaning to this phenomenon. In fact, the flickering could be perceived during the switch between the shortly presented emotional expression and the clearly visible neutral masking expression due to slight details changing in the face as the position of the eyebrows and/or mouth. For comparison, the transition between the facial stimuli and the scrambled image was clearly visible and was thus not perceived as a flickering.

For data analysis, the paradigm outlined above was considered to represent two different time intervals referring to Svenson's distinct decision steps (Svenson, 1996). Being presented with the facial stimuli (or the scrambled images in the control condition, respectively) represented the pre-decision phase since the subjects were already aware they were required to make decisions based on the pictures they were presented with. The instruction to choose one out of two adjectives in order to indicate which was a closer match to the facial expression seen before thus prepared subjects for the subsequent decision, in our paradigm the moment they pressed the response button. Accordingly, in the control condition, when only scrambled images were presented, decisions had to be made based on instructions on screen. Thus, beyond brain areas related to visual or face processing and associated mental processes also brain areas related to decision making should become engaged. Visual processing of the word list, the selection of the active finger and the button press were identical in both conditions.

The "pictures of facial affect" dataset is one of the most intensively studied facial expression datasets of all times (e.g. Adolphs, 2002; Seitz *et al.*, 2008). It contains expressions of six basic emotions, as

well as a neutral reference expression of male and female actors. All neutral faces used as masks in the current study were previously rated neutral in a pre-study with 30 volunteers. In the pre-study, the participants were required to rate whether a presented facial expression represented one of the six basic emotions (anger, sadness, fear, disgust, happiness, surprise) or a neutral expression and to which degree (measured in percent) the expression represented each of the emotions or neutrality. In addition, the emotional adjectives used as the response criteria were matched for word frequency, perceived arousal and dominance (SAM, Bradley & Lang, 1994) based on data from another pre-study in 44 volunteers.

Scanning parameters
Scanning was performed on a 3 T Siemens Trio TIM MRI scanner (Erlangen, Germany) using an EPI-GE sequence (TR = 2000 ms, TE = 30 ms, flip-angle = 90°). The whole brain was covered by 28 transversal slices oriented parallel to the bi-commissural plane (in-plane resolution = 1.5 mm × 1.5 mm, slice thickness = 4.0 mm, interslice gap = 0 mm). In each run, 1200 volumes were acquired. The first three volumes of each session did not enter the analysis. A 3D-T1-weighted image (gradient echo sequence) with high-resolution consisting of 192 sagittal slices and 1 mm × 1 mm resolution was also acquired in each subject (TR = 2300 ms, TE = 2.98 ms, flip angle = 90°).

FMRI scanning was followed by approximately 6 min of anatomical scanning. Post-scanning, participants rated all stimuli on the dimensions arousal, valence and dominance (SAM, Bradley & Lang, 1994) and were debriefed about the experiment.

Data processing and analysis
Behavioral data analysis
Behavioral data were analyzed using SPSS software PASW, Predictive Analysis Software, version 20). Prior to analysis, all statistical data were tested for normal distribution using Kolmogorov-Smirnov test. For comparison of means, single factor analyses of variance (ANOVA) were used.

FMRT data analysis
The Brainvoyager QX software package (Brain Innovation, Maastricht, The Netherlands) was used for the analysis of imaging data. Functional data were pre-processed including Gaussian spatial smoothing (FWHM = 8), temporal filtering, removal of linear trends and movement correction. In each subject, the 2-D slice time-course image data were co-registered with the volumetric 3-D Gradient Echo data sets from the same session.

We analyzed the blood oxygenation level dependent (BOLD) changes in a mixed rapid event-related model and entered the planned contrasts in a random effects group analysis. The whole-brain analysis was based on a general linear model (GLM) and a deconvolution approach which allowed the capturing of event-related brain activity at different time steps after event onset, estimating the hemodynamic response function (HRF). The third volume (4000 ms after event onset) was chosen in order to map activation patterns when the blood oxygen dependent (BOLD) increase was close to peak. The separation of the two defined decision phases was possible by the event-related character of the scanning procedure in which

the two events of interest were separated in later data analysis by applying a temporal jitter (temporal separation of pre-decision and decision was 2.600 ms on average) using a scanning repetition time of 2000 ms. In this exploratory study, clusters of activations were considered significant when they surpassed a p < 0.005 and had a minimal cluster size of 405 voxels in 3D space (equivalent to 15 cohesive voxels). This procedure corrects for the limited spatial resolution and the autocorrelation of adjacent voxels in the fMRI images and for multiple comparisons (Knorr *et al.*, 1993; Worsley *et al.*, 1992). The following regressors were included: *baseline, pre-decision phase, decision phase,* and *motor control*. Scrambled faces (generated by a self-programmed software) served as the baseline condition, and motor control reflected a simple motor response task (reacting towards an unrelated target word out of two words) in order to subtract motor and reading related activity.

In addition to the whole brain analysis, the activated clusters in the DLFC during the preparatory decision phase as well as the decision itself were defined as regions of interest (ROI) in order to extract their parameter estimates (β) for statistical comparison of the degree of activation between conditions. To ensure comparability with data in the open literature, we defined all activated regions within the DLFC as ROIs with a maximum cluster spread range of 10 mm around the peak of activation. All coordinates are given as peak coordinates in stereotactic space (Talairach & Tournoux, 1988).

Functional connectivity analyses

We used meta-analytic connectivity modeling (MACM) to explore the task-based functional connectivity of the two ROIs identified in this study in the DLFC. After identification of all experiments in the BrainMap database (www.brainmap.org; Laird *et al.*, 2011; Laird *et al.*, 2009) which report activation of the seed regions, quantitative meta-analysis permitted testing for convergence across the clusters of activation reflecting co-activation with the seed regions (Eickhoff *et al.*, 2010). Our analysis was based on approximately 7500 experiments from the BrainMap database reflecting functional mapping studies involving group analyses on healthy participants. Importantly, in order to ensure a completely data-driven approach, all experiments fulfilling the above-mentioned criteria of the BrainMap database were included regardless of behavioral classification. In a first step, all experiments reporting foci within a 5 mm radius of the seed regions were identified (Cieslik *et al.*, 2011; Eickhoff *et al.*, 2011a), followed by activation likelihood estimation (ALE) to discover co-activations across experiments (Eickhoff *et al.*, 2010; Eickhoff *et al.*, 2009). Importantly, ALE is based on the assumption that the reported foci are not single points but function as centers for 3D Gaussian probability distributions considering the focus-related spatial uncertainty using an empirical model of between-subject and between-template variance (Eickhoff *et al.*, 2009). Voxel-wise combination of the probabilities related to all foci then permitted creating modelled activation (MA) maps (Turkeltaub *et al.*, 2012). These were subsequently merged in order to get voxel-wise and noise-corrected ALE-scores representing the concordance of results at a family-wise error (FWE) corrected p-threshold of p < 0.05 (Eickhoff *et al.*, 2012).

In a further step, difference maps contrasting functional connectivity maps of the two defined DLFC ROIs were obtained based on their voxel-wise differences as extracted from their MACM-maps.

Subsequently, two groups of experiments were formed by pooling and randomly assigning them to same-size groups (Eickhoff *et al.*, 2011b). A repeated (10,000 times) subtraction of the group's voxel-wise ALE-scores resulted in an empirical null distribution of ALE-score differences between the two conditions. This was followed by thresholding the map of true differences at a probability of p > 0.95 for a true difference between both. To avoid false positive voxels, the resulting maps were masked with the respective main effect of the minuend connectivity map and the minimal cluster size was 20 cohesive voxels. Thus, in order to show the differences of the connectivity patterns for the two regions in the dorsolateral frontal cortex as obtained from our fMRI-experiment, an empirical null distribution was calcutated by the repeated subtraction of the randomly paired ALE-score maps of the approximately 7500 experiments from the BrainMap database. The noise characteristic of this null distribution map was used subsequently as a reference for thresholding the map of the true ALE-score differences of the two connectivity patterns at p < 0.05.

Statistical data of subareas of the dorsolateral frontal cortex in socially relevant decisions based on masked affect expressions

2 Data Files

http://dx.doi.org/10.6084/m9.figshare.1153792

Results

The fMRI study was preceded by a behavioral study in 32 healthy subjects (mean age 23.9 years, SD = 2.3) testing whether the experimental manipulation was successful (cf. Prochnow *et al.*, 2013b). We found that the subtle masked facial expressions of emotion affected the adjective choice and were thus suitable for a study on decision-making (for a detailed description of the statistical results, please refer to Prochnow *et al.*, 2013b).

We first present the activation patterns obtained by whole-brain analysis with emphasis on the masked facial expressions of emotion at the pre-decision phase and the subsequent actual decision. Second, we report the comparisons based on the regionally extracted parameter estimates (β) for the two activated areas in DLFC. And finally, we describe the functional connectivity of these seed regions in DLFC.

Activation patterns in whole brain analysis

Pre-decision phase: masked facial expressions vs. baseline. In the pre-decision phase, comparing masked emotional facial expressions with scrambled images of faces (baseline) resulted in a bilateral activation of the occipital cortex extending to the fusiform gyrus, of the caudal intraparietal sulcus, as well as of the right superior temporal sulcus, left premotor cortex and most importantly of a right posterior portion of the DLFC (*x = 44, y = 16, z = 27,* Figure 1).

Decision phase: decisions based on masked affect expressions vs. motor control. At the moment of the actual decision as indicated by the subjects choice of one of two emotional adjectives following a masked emotional face, we found activation of the left cuneus, left putamen, left paracingulate gyrus, right inferior frontal gyrus and, most importantly, of an anterior portion of the right DLFC (*x = 50, y = 28, z = 36,* Figure 1).
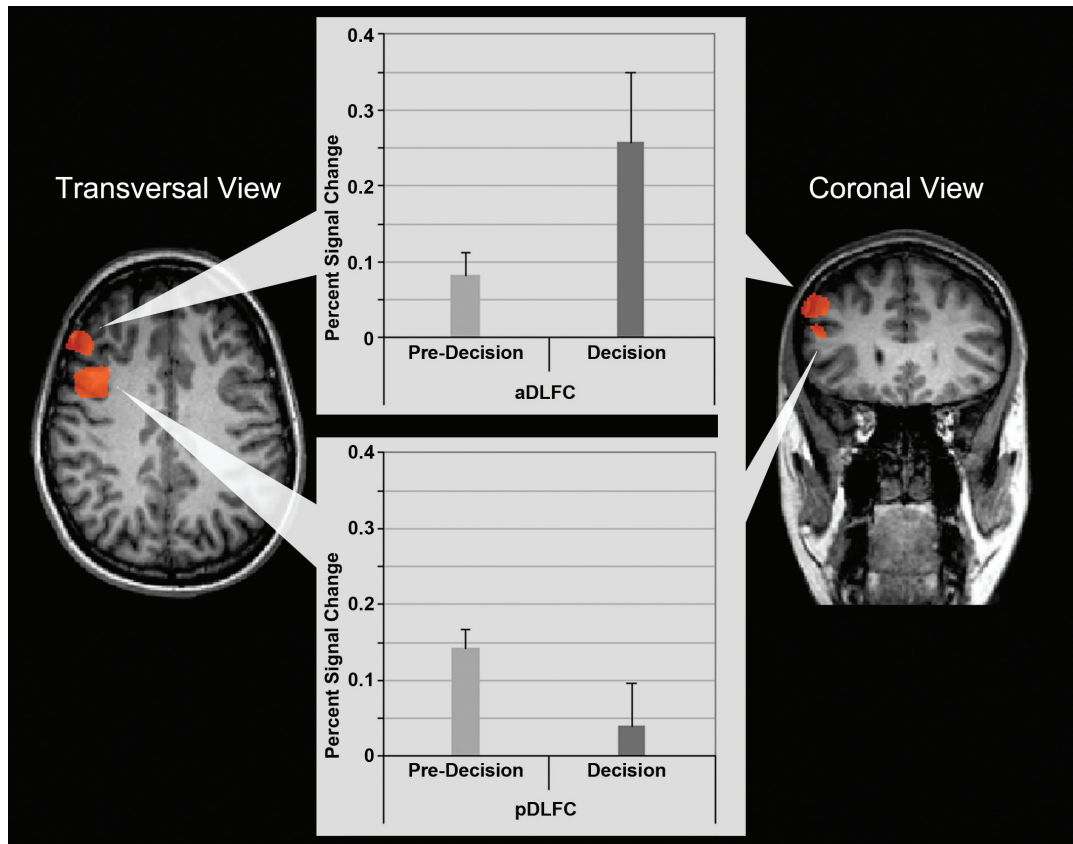
Figure 1. Location of the activated brain regions in DLFC that became activated in the pre-decision phase (pDLFC) and during the subsequent decision (aDLFC). These activation clusters were used to define regions of interest based on their activation peaks plus a cluster spread range of 10 mm. The diagrams show their degrees in percent signal change at both events of interest.

Region of interest (ROI) analysis. The activation peak of the ROI related to *pre-decisional masked face presentation* was located posterior within the DLFC, while the activation peak of the ROI related to the *decision phase* was located more anterior with a Euclidean distance of 16.16 mm to the ROI related to *pre-decisional masked face presentation*. This distance exceeded the spatial resolution of the fMRI images (8 mm full width and half maximum (FWHM)).

We conducted pairwise t-tests to compare parameter estimates between the two DLFC ROIs (for their definition see the Materials and methods section) at $\alpha = 0.05$, and additionally calculated effect sizes (Cohen's d) due to the small sample size. The parameter estimates related to *pre-decisional masked face presentation* did not differ significantly from those during the *decision phase* (T = -1.02, df = 11, p = 0.329; Cohen's d = 0.2).

Correlation analyses revealed that no correlation was found between parameter estimates related to *pre-decisional masked face presentation* and the *decision phase*. Notably, the parameter estimates of the *decision phase of the masked emotional faces* correlated significantly with the accuracy of related decisions following sad expressions. However, parameter estimates in none of the defined DLFC ROIs correlated with self-reported empathy (SPF questionnaire), mood (BDI, Hautzinger *et al.*, 1994) or emotional competence (TAS-20, Bagby *et al.*, 1994).

Functional connectivity analyses. This hypothesis-free meta-analytic approach capitalized on the large BrainMap database for calculating statistical maps of co-activation for these two seed regions. For their computation using ALE-based meta-analysis, the posterior ROI related to *pre-decisional masked facial expressions* and the anterior ROI related to the actual *decision phase* in the DLFC were used as seed regions. Both were associated with bilateral co-activations in the DLFC and the adjacent premotor cortex. Also, there was task-dependent co-activation in the dorsomedial frontal cortex and around the intraparietal sulcus which was found bilaterally in relation to the seed region associated with *pre-decisional masked facial expressions* and exclusively right-sided regarding the seed region representing the subsequent *decision phase*. In addition, the seed region in the DLFC related to *pre-decisional masked facial expressions* featured co-activations in the inferior frontal gyrus bilaterally and in the left fusiform gyrus.

The conjunction between co-activations related to both DLFC seed regions comprised two clusters of co-activations in the DLFC, one located more anterior and the other more posterior, a cluster in the left intraparietal sulcus and a cluster in the dorsomedial frontal cortex which included parts of the pre-supplementary motor area (pre-SMA) (Figure 2).
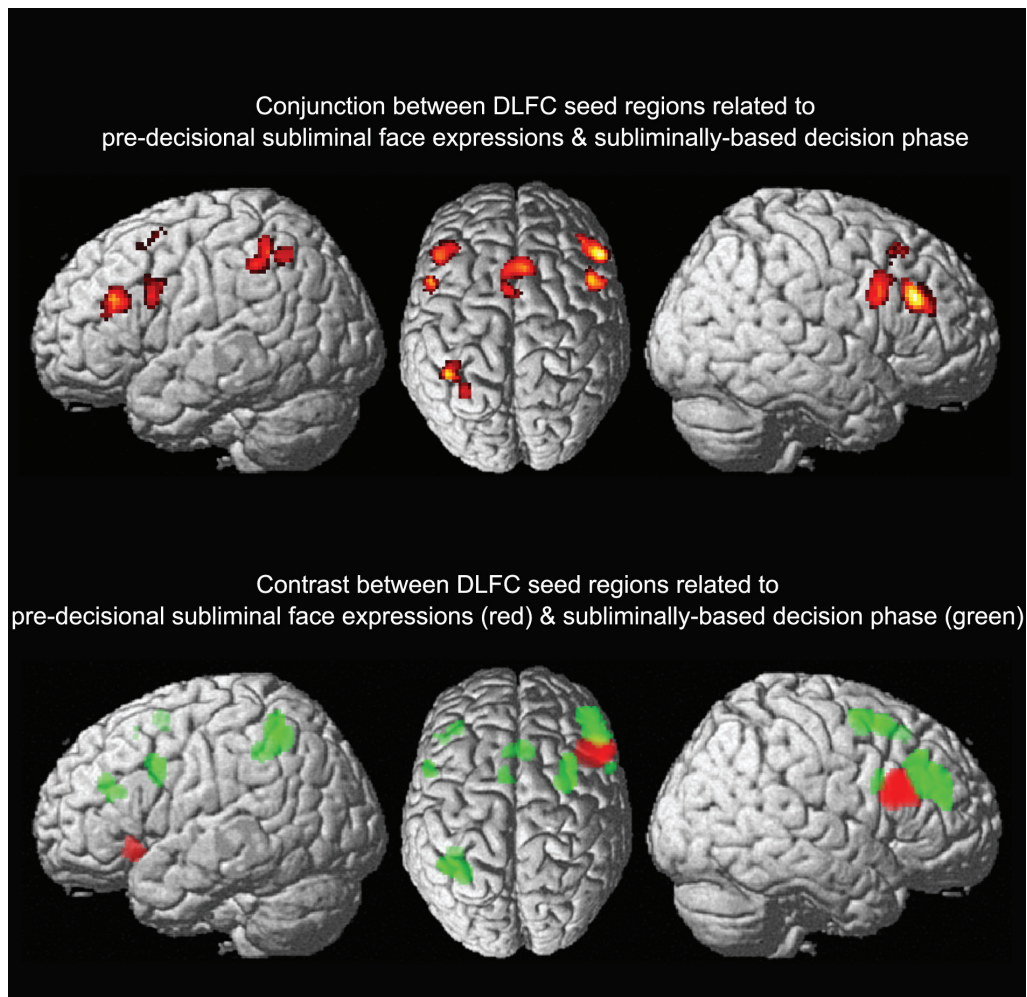
Figure 2. Co-activation maps of the conjunction of co-activations related to the two DLFC seed regions (top), and the difference maps related to the pre-decisional masked facial expressions (bottom red) and the subsequent related decision phase (bottom green).

Contrasting the co-activation patterns between the two seed regions yielded a more distributed pattern of co-activated clusters in relation to the DLFC seed region associated with the *decision phase*. This seed region featured stronger co-activations in the left and right DLFC, the adjacent premotor cortex, the dorsomedial frontal cortex, the left pre-SMA and around the left intraparietal sulcus (Figure 2). Interestingly, the seed region in relation to the *decision phase* was associated with stronger co-activations in two distinct DLFC clusters bilaterally, an anterior and a posterior one, whereas the seed region of *pre-decisional masked facial expressions* featured a stronger co-activation in a right DLFC region located between these two clusters. Also, it was associated with stronger co-activations in the right inferior frontal gyrus (Figure 2).

Discussion

This study aimed at identifying the brain areas related to different aspects of decision-making based on masked emotional information that presented a model of daily interpersonal interactions. Specifically, we used a paradigm capable of distinguishing the activation patterns during a preparatory decision phase when not all decision-relevant information was present, from activation patterns related to the decision itself. We found the right DLFC to be involved in both decision stages at clearly different positions: a posterior portion became activated when the actual decision was made as indicated by the subject's button press (*decision*). The *pre-decision phase* during which the subjects were presented with masked emotional facial expressions, which they had to evaluate later, was associated with an activation increase in the right anterior DLFC. No significant differences were found in the degree of activation between both sub-regions, as indicated by the extracted parameter estimates.

There is a large body of evidence implicating the DLFC in decision-making tasks (Basten *et al.*, 2010; Domenech & Dreher, 2010; Gilbert *et al.*, 2010; Hall *et al.*, 2010; Hayama & Rugg, 2009; Hosseini *et al.*, 2010; Huettel & Misiurek, 2004; Plassmann *et al.*, 2007), especially when the decisions are characterized by some degree of ambiguity (Christakou *et al.*, 2009; Kahnt *et al.*, 2011; Krain *et al.*, 2006). Moreover, DLFC activity has been found in

various higher-order cognitive tasks such as working memory and monitoring tasks (Durston *et al.*, 2003; Kellermann *et al.*, 2012; Opitz *et al.*, 2000; Wagner *et al.*, 2001) and cognitive control tasks (Cieslik *et al.*, 2010; Cole & Schneider, 2007; Eickhoff & Grefkes, 2011; Jakobs *et al.*, 2009; Milham *et al.*, 2003). These are considered pre-dominantly "cold" cognitively-driven tasks (Zelazo & Muller, 2002) and may act as key players in self-related control tasks such as decision-making and choice (reviewed by Banfield *et al.*, 2004).

However, even though affect-based decisions have been traditionally linked to the recruitment of the ventromedial and orbitofrontal prefrontal cortex, which we failed to observe in the current study (Chib *et al.*, 2009; Grabenhorst & Rolls, 2011; Krain *et al.*, 2006; Smith *et al.*, 2010; Zelazo & Muller, 2002), we consistently found DLFC activation in affective judgment tasks (Prochnow *et al.*, 2013a; Prochnow *et al.*, 2013b; Prochnow *et al.*, 2014b). Our observations are supported by studies using affective tasks which implicitly studied decisions in an affective context (Bzdok *et al.*, 2012a; Lawrence *et al.*, 2006; Opialla *et al.*, 2015; Silvers *et al.*, 2015; Thirioux *et al.*, 2014; Walter *et al.*, 2004). In order to model daily interpersonal interactions we intentionally created a decision-making paradigm in which the subjects had to base their decisions on subtle and thus ambiguous facial expressions. Following the affective primacy hypothesis (Murphy & Zajonc, 1993), the emotional expressions were considered to elicit an affective response in the observer even though the subjects were not aware of having seen them, similarly as to what Ekman has described as micro expressions (Ekman, 1992; Shen *et al.*, 2012). The short emotional expression was thus expected to add an emotional flavor onto the masking neutral expression which loaded an ambiguous stimulus with a specific emotional state (Rohr *et al.*, 2012; Prochnow *et al.*, 2013b).

In the current study, as well as in previous studies (Prochnow *et al.*, 2013b; Prochnow *et al.*, 2014b), we show that already during the presentation of *pre-decisional masked facial expressions* a posterior and more ventral portion of the DLFC became activated. According to anatomical coordinates, this activation cluster corresponded to dorsolateral frontal regions found in normative decision-making (Baumgartner *et al.*, 2011) and ill-structured problem-solving (Gilbert *et al.*, 2010), indicating its importance in the decision-making process. During this preparatory stage of decision-making, when not all necessary information to make a goal-directed decision is present, Svenson's theory assumes that calculation of decision values takes place (Svenson, 1996). Evidence for the involvement of the DLFC in the calculation of decision values comes from a growing number of studies (Camus *et al.*, 2009; Litt *et al.*, 2011; Plassmann *et al.*, 2007; Sokol-Hessner *et al.*, 2012). Notably, a more anterior and dorsal portion of the DLFC became activated when the adjectives offered as the decision criteria were presented and the subjects had to make a decision (forced choice paradigm). This result is in line with our previous study showing anterior DLFC engagement during online emotion discrimination and categorization (Prochnow *et al.*, 2013a) and suggests that the anterior portion of the DLFC is associated with uncertain decisions (Hosseini *et al.*, 2010).

DLFC activations reported in the literature are heterogeneous in their locations and also regarding their related tasks. Most clusters are situated in close proximity to the anterior cluster found

here or even more anterior. Functionally, they are referred to working memory and monitoring (Rottschy *et al.*, 2012; Wagner *et al.*, 2001), self-reflection (Herwig *et al.*, 2012), cognitive control or cognitive conflict (Cieslik *et al.*, 2010; Eickhoff & Grefkes, 2011; Jakobs *et al.*, 2009; Milham *et al.*, 2003) and different aspects of decision-making (Krain *et al.*, 2006; Plassmann *et al.*, 2007; Prochnow *et al.*, 2013a). Especially, there seems to be a conceptual overlap of studies examining cognitive control, cognitive conflict and decision-making depending on the focus of the study. Whereas studies focusing on decision-making, including the current study, implicitly study aspects of cognitive control, studies on cognitive control appear to imply aspects of decision-making. In order to get further insights into the functional connectivity of the DLFC, this study also focused on the identification of co-activations of the two subareas within the DLFC obtained in the whole brain analysis.

The analyses of functional connectivity showed that the posterior DLFC cluster activated during the *pre-decision phase* featured stronger co-activations in the right inferior frontal gyrus (IFG) and in a DLFC area located between the precentral and inferior frontal sulcus. By contrast, the anterior portion of the DLFC that became activated during the *actual decision* was associated with stronger co-activations in two DLFC areas framing the DLFC region co-activated in relation to the posterior DLFC seed region. In addition, it featured co-activations of the premotor cortex, a dorsomedial frontal region, the left pre-SMA and the left intraparietal sulcus. Activation of the IFG has been found repeatedly in tasks involving low-level empathy (Carr *et al.*, 2003; Lamm *et al.*, 2007; Lindenberg *et al.*, 2012; Prochnow *et al.*, 2013a; Schulte-Rüther *et al.*, 2007; Seitz *et al.*, 2008; Shamay-Tsoory *et al.*, 2009), most likely because it is considered an important node of the putative human mirror neuron system (Rizzolatti & Craighero, 2004). Moreover, the left IFG is well known to accommodate Broca's speech area (Lindenberg *et al.*, 2007) and its activation might therefore also reflect covert speech. Accordingly, in our paradigm one would expect left IFG activity to co-occur during the *actual decision* since at this stage, the subjects were confronted with verbal descriptions in form of two emotional adjectives they were required to choose in order to respond. Instead, the whole brain analysis showed an activation increase in the right inferior frontal gyrus during the *actual decision*, and neither the *pre-decision phase*, nor the *actual decision* was associated with an activation increase in the left IFG in this sample. However, although the *pre-decision phase* does not involve any explicit speech component, it remains impossible to control for covert speech in fMRI tasks like ours.

Interestingly, in the current study activity in the anterior portion of the DLFC associated with the *actual decision* was also accompanied by an activation increase in the left paracingulate gyrus. This dorsomedial prefrontal region has been found relevant for rapid interpersonal evaluations (Cooper *et al.*, 2012) and theory of mind (Hooker *et al.*, 2008; Schulte-Rüther *et al.*, 2007). Moreover, the adjacent pre-SMA has been shown to be crucial in the context of the generation of the so-called Bereitschaftspotential to perform a movement (Shibasaki & Hallett, 2006), as well as for movement selection (Deiber *et al.*, 1991; Hoffstaedter *et al.*, 2013). Interestingly, it was not only found active during the recognition of emotions in static emotional facial expressions (Seitz *et al.*, 2008) but also when dynamically evolving emotional facial expressions had to be discriminated (Prochnow *et al.*, 2013a). These observations

suggest that the dorsomedial portion of the prefrontal cortex including the adjacent pre-SMA becomes involved when an external mental state needs to be transferred into an internal frame of reference (Seitz *et al.*, 2006; Seitz *et al.*, 2009).

In addition to the identification of different patterns of functional connectivity between the posterior DLFC region related to the *pre-decision phase* and the anterior region related to the *decision phase*, we were interested in the co-activations shared by both DLFC regions. These were bilateral anterior and posterior areas in the DLFC, the dorsomedial frontal cortex including the pre-SMA and the left intraparietal sulcus, suggesting a common network allowing for visuo-spatial and time-related attention (Culham & Kanwisher, 2001; Davranche *et al.*, 2011; Grefkes & Fink, 2005) and self-referential valuation (Seitz *et al.*, 2006; Seitz *et al.*, 2009).

In the current study, activations of the two subregions in the DLFC were clearly lateralized to the right cerebral hemisphere featuring co-activations distributed over both hemispheres. This result corresponds to behavioral evidence showing that not consciously accessible faces affected choices regardless of the visual hemifield to which they were presented while, in contrast, subliminally presented words affected choices only when they were presented to the left cerebral hemisphere (Henke *et al.*, 1994).

Possible limitations of the current study should not go unmentioned. We considered the moment when our subjects viewed the emotional masked facial expressions the preparatory stage of the actual decision since not all relevant information was present to make a goal-directed choice. It cannot, however, be ruled out that instead of measuring a pre-decision phase and the actual decision, there were two different decisions following one-another. A first partial decision based on only the visual information and the outside of subjective awareness elicited affective response and a subsequent decision when the emotional adjectives as the decision criterion were available. For example, Wunderlich *et al.* (2010) provided evidence that people are able to partially make a choice in stimulus space before knowing the motor mapping associated with the final decision. Independent of these theoretical considerations, our fMRI and functional connectivity data showed that both time points were associated with the involvement of different parts of the DLFC indicating functional specialization in the DLFC. Instead of representing a pre-decision phase and the decision itself, the anterior-posterior subdivision could also reflect different degrees to which the decision was goal-directed. Moreover, we used scrambled versions of the digitzed images of the faces as baseline that had been corrected for luminescence, as they were as much as possible identical to the faces except for their appearance. They were scrambled images of the emotional faces in the unmasked condition and scrambled images of the emotional faces followed by scrambled images of the neutral faces in the masked condition. Notably, neutral faces were not appropriate for baseline, since we used images of faces that had been classified as neutral (Prochnow *et al.*, 2013b) for masking of the emotional face expressions. Moreover, distorted faces or face-like objects would introduce visual features that would attract the subjects' attention in a strong and poorly controlled fashion, since they are strong visual stimuli (Dalrymple *et al.*, 2014; Freeman *et al.*, 2010). Thus, we believe that in the pre-decision phase our paradigm was focussed on the processing of emotional face expressions. Finally, in our event-related protocol we sought to separate the hemodynamic response related to the emotional face expressions in the pre-decision phase from the hemodynamic response related to the verbal stimuli in the decision phase in one experimental paradigm. For this purpose these two visual stimuli were separated by a blank of 2600 ms on average which was jittered between 400 and 4800 ms. Given a TR of 2000 ms this interval was sufficiently long to detect the two different hemodynamic responses, since event-related fMRI can resolve subsequent hemodynamic responses with a separation of as little as 200 to 400 ms (de Zwart *et al.*, 2009).

Conclusions

In conclusion, our data suggest that the DLFC is crucial for decisions involving masked, and thus, ambiguous affective information. Moreover, by use of categorical and functional connectivity image analysis approaches we provide evidence for partially independent sub-regions within the right DLFC. Whereas the posterior portion of the right DLFC was relevant for the preparatory phase within the decision process when not all the necessary information for a goal-directed choice were available, the anterior sub-region appeared to be related to later goal-directed decision stages involving sustained attention for time, space and valuation. These results may be related to the notion of dual associative processes in intuitive judgments (Morewedge & Kahneman, 2010).

Participant consent

All participants gave informed written consent to participate in the fMRI study. Experiments were approved by the local ethics committee and conducted according to the Declaration of Helsinki.

Data availability

figshare: Statistical data of subareas of the dorsolateral frontal cortex in socially relevant decisions based on masked affect expressions. Doi: 10.6084/m9.figshare.1153792 (Prochnow *et al.*, 2014a).

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Open Peer Review

Current Referee Status: ☑ ☑

Version 3

Referee Report 27 July 2015

doi:10.5256/f1000research.7214.r9430

Gonzalo G de Polavieja
Neuroscience Programme, Champalimaud Foundation, Lisbon, Portugal

I am happy with the addition in the Limitations section and with a better description of the controls. I still think in future studies other controls can be added with procedures that still leave face-like features but eliminate affect expressions.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Referee Report 13 July 2015

doi:10.5256/f1000research.7214.r9457

Motoaki Sugiura
Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Version 2

Referee Report 14 May 2015

doi:10.5256/f1000research.6841.r8390

Gonzalo G de Polavieja
Neuroscience Programme, Champalimaud Foundation, Lisbon, Portugal

I thank the authors for careful consideration of my previous comments. However, I still think that my main concern remains. The comparison of the reaction to faces against scrambled images is not enough to conclude that the difference in activation is due to faces. It could well be due to any characteristic in the 'faces' class not present in the 'scrambled' class, like smoothness or local contrast values. They mention in their response that scrambled images are are 'suited to maximize the cognitive comparison to faces'. Quite the opposite, you would need a control class that has as much as possible from the 'faces' class except the appearance of faces, probably several classes of distorted faces as well as your present control.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.

Reader Comment 21 Jun 2015

Denise Prochnow, Heinrich Heine University Dusseldorf, Germany

Dear Dr. de Polavieja,

we thank you for reviewing our manuscript a second time and for your constructive criticism.

Concerning the point raised by you and the other reviewer we elaborated further on the description of the face stimuli and their scrambled versions. Also, we explain that the type of stimuli we used in our study have been used by other authors for the same purpose as in our study as well; we refer to them. Furthermore, we now discuss our approach in the limitation section as suggested by the reviewers.

Specifically we made the following changes in the Methods: *… Presented were just the faces while the remaining parts of the heads including the hair and ears were conceiled by the blank of the background….Also, we used scrambled versions of the face images to measure baseline as typically used to map the cerebral areas spefically related to face perception (Slotnik and White 2001, Zhu et al 2013). These scrambled images were produced from the digitized images of the faces used and corrected for luminescence. Thus, the scrambled images had the same visual features as the images of the faces and were presented in an identical manner as the faces. Specifically, the scrambled images of the emotional faces were presented for 400ms in the unmasked condition, while the scrambled images of the emotional faces were presented for 40ms followed by presentation of the scrambled images of the neural faces for 360 ms in the masked condition…..*

In the final paragraph of the discussion we inserted the following paragraph*: Moreover, we used scrambled versions of the digitzed images of the faces as baseline that had been corrected for luminescence, as they were as much as possible identical to the faces except for their appearance. They were scrambled images of the emotional faces in the unmasked condition and scrambled images of the emotional faces followed by scrambled images of the neutral faces in the masked condition. Notably, neutral faces were not appropriate for baseline, since we used images of faces that had been classified as neutral (Prochnow et al. 2013b) for masking of the emotional face expressions. Moreover, distorted faces or face-like objects would introduce visual features that would attract the subjects' attention in a strong and poorly controlled fashion, since they are strong visual stimuli (Freeman et al. 2010, Dalrymple et al. 2014). Thus , we believe that in the*

pre-decision phase our paradigm was focussed on the processing of emotional face expressions.

We hope our manuscript is now acceptable for final publication.

Kind regards,
the authors

Competing Interests: No competing interests to disclose.

Referee Report 28 April 2015

Motoaki Sugiura
Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan

This reviewer is happy with the authors' effort on the revision and the resulting significant improvement of the manuscript. However, several important issues are remained unanswered, as follow:

For point 1, the authors clarified that the two contrasts do represent the cognitive process of their interest (i.e., two components of decision making process) but failed to provide reasonable defense against the contamination of the process of no interest, which was the point of this reviewer's criticism; for example, as the reviewer 1 has also pointed out, the contrast against the scrambled face includes many decision-irrelevant processes including object or face perception. The authors have to explain the reason to believe that the two contrasts predominantly reflect the process of their interest rather than other confounding factors, and also describe the unfavorable possibility as a limitation in the Discussion section.

For point 3, the reasons for the difference between the case 1 and case 2 are understandable, but not for the case 3. Please provide the reason for the necessity of Monte-Carlo-like simulation. In addition, please provide these reasons also for readers explicitly in the manuscript.

For point 4, considering the slow hemodynamic-response "temporal separation of 2.600 ms on average" is obviously insufficient to make two time-series models independent, regardless of the scanning TR. Here the detailed information on the range of jittering is important, and this limitation caused by this insufficient separation should be declared in the Discussion section

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.

Reader Comment 21 Jun 2015
Denise Prochnow, Heinrich Heine University Dusseldorf, Germany

We thank you for your constructive critics to our manuscript which stimulated us to make corresponding changes in a second revision. Please find below a list of the changes we made based on your review.

Concerning the point raised by you as well as the other reviewer, we elaborated further on the description of the face stimuli and their scrambled versions. Also, we explain that the type of stimuli we used in our study have been used by other authors for the same purpose as in our study as well; we refer to them. Furthermore, we now discuss our approach in the limitation section as suggested by the reviewers.

Specifically we made the following changes in the Methods: *… Presented were just the faces while the remaining parts of the heads including the hair and ears were conceiled by the blank of the background….Also, we used scrambled versions of the face images to measure baseline as typically used to map the cerebral areas spefically related to face perception (Slotnik and White 2001, Zhu et al 2013). These scrambled images were produced from the digitized images of the faces used and corrected for luminescence. Thus, the scrambled images had the same visual features as the images of the faces and were presented in an identical manner as the faces. Specifically, the scrambled images of the emotional faces were presented for 400ms in the unmasked condition, while the scrambled images of the emotional faces were presented for 40ms followed by presentation of the scrambled images of the neural faces for 360 ms in the masked condition…..*

In the final paragraph of the discussion we inserted the following paragraph*: Moreover, we used scrambled versions of the digitzed images of the faces as baseline that had been corrected for luminescence, as they were as much as possible identical to the faces except for their appearance. They were scrambled images of the emotional faces in the unmasked condition and scrambled images of the emotional faces followed by scrambled images of the neutral faces in the masked condition. Notably, neutral faces were not appropriate for baseline, since we used images of faces that had been classified as neutral (Prochnow et al. 2013b) for masking of the emotional face expressions. Moreover, distorted faces or face-like objects would introduce visual features that would attract the subjects' attention in a strong and poorly controlled fashion, since they are strong visual stimuli (Freeman et al. 2010, Dalrymple et al. 2014). Thus , we believe that in the pre-decision phase our paradigm was focussed on the processing of emotional face expressions.*

Concerning Point 3 we would like to explain that we used a conservative threshold for the fMRI activations found in our experiment. Similarly, for the MACM analysis we used a conservative threshold of $p<0.05$ corrected for family-wise errors as described earlier by Eickhoff et al. (2012). Also for the difference maps we used a corrected $p<0.05$. Given the different spatial characteristics of the difference maps as compared to the ALE score maps this correction was normalized to the intrinsic image noise of the difference maps both in terms of signal amplitude and spatial extent. Again, we refer to a recent publication in which this procedure was described in detail. To account for the comment of the reviewer we made the following addition in the methods: *Thus, in order to show the differences of the connectivity patterns for the two regions in the dorsolateral frontal cortex obtained from our fMRI-experiment, an empirical null distribution was calcutated by the repeated subtraction of the randomly paired ALE-score maps of the approximately 7500 experiments from the BrainMap database. The noise characteristics of this null distribution map was used subsequently as a reference for thresholding the map of the true ALE-score differences of the two connectivity patterns at $p < 0.05$.*

Concerning Point 4 we specified our description of the stimuli in the methods and added this information also to the final paragraph of the discussion where we describe in detail the imaging

characteristics of our study both concerning the temporal separation of the two stimuli and the scanning sequence. We refer to evidence in the open literature showing that fMRI is a powerful method to separate different events with a resolution of 200 to 400 ms. Specifically we adde the following sentences: *Finally, in our event-related protocol we sought to separate the hemodynamic response related to the emotional face expressions in the pre-decision phase from the hemodynamic response related to the verbal stimuli in the decision phase in one experimental paradigm. For this purpose these two visual stimuli were separated by a blank of 2600 ms on average which was jittered between 400 and 4800 ms. Given a TR of 2000 ms this interval was sufficiently long to detect the two different hemodynamic responses, since event-related fMRI can resolve subsequent hemodynamic responses with a separation of as little as 200 to 400 ms (de Zwart et al. 2009).*

We hope our manuscript is now acceptable for indexation.

Competing Interests: No competing interests to disclose.

Version 1

Referee Report 03 March 2015

Gonzalo G de Polavieja
Neuroscience Programme, Champalimaud Foundation, Lisbon, Portugal

The authors use fMRI experiments to argue that the dorsolateral frontal cortex (DLFC) responds in decision-making to masked affect human faces.

1. The reference images for the pre-decision phase are scrambled images. Scrambled images have a number of obvious features as they are not (a), faces, (b) smooth and (c) they have local contrast different to faces. So it is not obvious to me why the experimental condition, respect to this baseline, corresponds to affect faces, and not more generally to (a) some structure of faces, (b) smooth figures or (c) particular contrast structures. Why wouldn't you need to use additional controls to eliminate these options? (i.e. normal faces or objects)

   Related to this, you mention that you eliminate the 26% of subjects that suspect the presence of emotional faces and that 78% reported flickering. Although I didn't understand whether this flickering came from real flickering or not, I could not find in the text whether some subjects could report seeing the transition from scramble image to face.

2. Some of the reported data (mean age, % subjects that suspect emotional faces, etc) are identical to Prochnow e*t al* 2013b, but I cannot find mention in the present ms that the data collected is the same than in Prochnow *et al* 2013b or that the subjects are the same. Is this the case? Please, clarify.

3. Data presented are comparison of means, but the data obtained is distributions. Did you find whether other parameters of the distributions for other brain regions were significant (median, mode, variance).

4. Is there individual variability? As you made many preliminary tests on subjects (for example, empathy), it would be very interesting to correlate these results with brain activations.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.

Reader Comment 11 Apr 2015
Denise Prochnow, Heinrich Heine University Dusseldorf, Germany

We thank you for reviewing our manuscript and for the constructive comments he made. Based on these, we revised our manuscript carefully in order to improve it. Please find below our point by point answers to your constructive criticism.

- You wrote *"The reference images for the pre-decision phase are scrambled images. Scrambled images have a number of obvious features as they are not (a), faces, (b) smooth and (c) they have local contrast different to faces. So it is not obvious to me why the experimental condition, respect to this baseline, corresponds to affect faces, and not more generally to (a) some structure of faces, (b) smooth figures or (c) particular contrast structures. Why wouldn't you need to use additional controls to eliminate these options? (i.e. normal faces or objects)"*

  We thank you for this important comment and would like to point out that scrambled images were used to subtract activation related to visual processing. As you correctly mention, scrambled images differ from facial images in smoothness and local contrast.They are identical in overall contrast and color but do not convey any face information or meaning. Thus, we consider they are suited to maximize the cognitive comparison to faces.

- You wrote *"Related to this, you mention that you eliminate the 26% of subjects that suspect the presence of emotional faces and that 78% reported flickering. Although I didn't understand whether this flickering came from real flickering or not, I could not find in the text whether some subjects could report seeing the transition from scramble image to face."*

  We thank you for this important point as well. Indeed, the majority of subjects reported having noticed a flickering throughout the experiment. As explained now in detail on page 5, this perception was due to the rapid succession of the emotional expressions presented below the threshold of subjective awareness and the clearly visible neutral masking expression. Please note that the subjects did not report a break but just a flicker which was due to the fact that there were only slight details changing in the face as the position of the eyebrows and / or mouth. For comparison, the transition between the facial stimuli and the scrambled image was clearly visible and was not perceived as a flickering.

- You wrote *"Some of the reported data (mean age, % subjects that suspect emotional faces, etc) are identical to Prochnow et al 2013b, but I cannot find mention in the present ms that*

the data collected is the same than in Prochnow et al 2013b or that the subjects are the same. Is this the case? Please, clarify."

We are also thankful for this important information. We now provide more detailed information on the relationship between both articles and explain that both are based on the same data set albeit studying entirely different aspects. Prochnow et al., 2013b compared brain activation patterns between facial expressions of emotion which were either clearly visible or presented below the threshold of subjective awareness and superimposed by a neutral masking facial expression. On the contrary, concerning the experimental paradigm the current article focuses on the decision aspect of the overall paradigm since the subjects were instructed to decide which of two subsequently presented emotional adjectives best described the mood observed in the previously seen face. Furthermore, this paper addresses the novel issue of functional connectivity of the activated lateral prefrontal cortex.

- You wrote *"Data presented are comparison of means, but the data obtained is distributions. Did you find whether other parameters of the distributions for other brain regions were significant (median, mode, variance)."*

  We have analyzed our fMRI data with established image analysis tools of BRAIN VOYAGER which computes t-tests on a voxel by voxel basis. A similar approach is utilized by MCAM ALE. Thus, we adhered to standards that have been developed for functional imaging data which allow to compared studies of different laboratories, since they are generally used.

- You wrote *"Is there individual variability? As you made many preliminary tests on subjects (for example, empathy), it would be very interesting to correlate these results with brain activations."*

  We thank you for mentioning this interesting aspect. We fully agree that this is an important issue. For that reason we extracted the local values in two areas of interest in the dorsolateral prefrontal cortex, our area of interest, to address this issue. Unfortunately, a study on the individual variability in an omnibus approach would be a study in its own right and go far beyond the present communication.

Competing Interests: No competing interests to disclose.

Referee Report 25 September 2014

Motoaki Sugiura
Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan

The authors tried to demonstrate that anterior and posterior subregions of the DLFC are involved in different phases (i.e., pre-decision and decision *per se*, respectively) of socially relevant decisions based on subliminal emotional information. The addressed issue is important in related fields and the approach is unique. However, I consider that the following methodological issues require clarification before the

evaluation of the work.

Major points:
1. Is it reasonable to use the contrasts "masked facial expressions vs. baseline" and "decisions based on masked affect expressions vs. motor control" to isolate the DLPF subregions for the socially relevant decisions based on subliminal emotional information? Activation identified in these contrasts may be affected by variety of perceptual and cognitive processes. How can the authors' assumption that activation in these contrasts reflected only the decision making process be justified?
2. Also, in the MACM approach, authors did not make the selection of the data based on the task or contrast. How, then, can the authors' argue the identified connectivity specifically reflected the decision making process?
3. The authors used 1) "$p < 0.005$ and minimal cluster size of 405 voxels" for the fMRI analysis, 2) "a family-wise error (FWE) corrected p-threshold of $p < 0.05$" for the MACM/ALE analysis, and 3) some Monte-Crlo-like simulation described after the explanation of 2. I don't understand the reason for using both 2 and 3 for the MACM/ALE analysis, and also see how adaptation of these three different thresholds/criteria across three cases was justified.
4. In the task, how can activation for the pre-decision and decision phases be separated despite the fixed close interval of the two phases?
5. Region of interest (ROI) analysis, paragraph 2 - "We conducted pairwise t-tests to…": Why was this uncommon analysis necessary?

Details:
- Introduction, paragraph 3, last sentence - "Recent evidence, however, suggests that gaming and ToM scenarios are based at least partly on different neural circuits": I don't get the nuance; was there an assumption that the gaming and ToM perfectly share the neural substrate?
- FMRT data analysis, paragraph 3 - "To ensure comparability…": I don't understand what is meant by "comparability" (i.e., with what?) or what has exactly been done here. In addition, authors should be clear about the "template" for the normalization; "Talairach space" sometimes means just a 3D brain space.
- Functional connectivity analyses, paragraph 1 - "above-mentioned criteria": which criteria do you mean?

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.

Reader Comment 11 Apr 2015

Denise Prochnow, Heinrich Heine University Dusseldorf, Germany

We thank you for reviewing our manuscript. Based on his thoughtful and constructive criticism, we revised our manuscript carefully and made the following changes. Please find below our point by point answers to the important comments you made.
- You wrote *"Is it reasonable to use the contrasts "masked facial expressions vs. baseline" and "decisions based on masked affect expressions vs. motor control" to isolate the DLPF subregions for the socially relevant decisions based on subliminal emotional information? Activation identified in these contrasts may be affected by variety of perceptual and*

cognitive processes. How can the authors' assumption that activation in these contrasts reflected only the decision making process be justified?"

We are thankful for this comment and now explain in more detail in the methods section the rationale behind our paradigm (p.5). In the first part of the visual stimulation, corresponding to the pre-decision phase, masked faces or scrambled faces were presented. They had the identical visual input. However, when the subjects were exposed to the faces they were tuned to do a subsequent decision, since they were instructed to choose one out of two emotional adjectives presented to them after the faces. Thus, beyond brain areas related to emotional face perception also brain areas related to decision making should become engaged. In the decision phase the subjects had to indicate the appropriate word describing the emotion seen previously in the masked face by a button press. In the motor control condition, the subject had to press the right or left button according to the visually presented instruction. Thus, visual processing of the word list, the selection of the active finger and the button press were identical in both conditions. However, the decision which word described the previously face was only present in the decision condition.

- You wrote *"Also, in the MACM approach, authors did not make the selection of the data based on the task or contrast. How, then, can the authors' argue the identified connectivity specifically reflected the decision making process?"*

We thank you for this point and added some information to the results section (p.9). In the MACM approach all experiments in the BrainMap database reporting activation of the seed regions were identified irrespective of their behavioral classification. From these data a quantitative meta-analysis was performed that tested the presence of activation clusters in the imaging data of the database resulting in a statistical map of co-activations with the seed regions. We agree with the reviewer that this analysis reflects the functional connectivity of the DLPF but does not the decision making process.

- You wrote *"The authors used 1) "p < 0.005 and minimal cluster size of 405 voxels" for the fMRI analysis, 2) "a family-wise error (FWE) corrected p-threshold of p < 0.05" for the MACM/ALE analysis, and 3) some Monte-Crlo-like simulation described after the explanation of 2. I don't understand the reason for using both 2 and 3 for the MACM/ALE analysis, and also see how adaptation of these three different thresholds/criteria across three cases was justified."*

We also thank you for your comment on our choice of statistical thresholds. The fMRI experiment was based on 18 healthy subjects. This statistical thresholding we used corresponds to established criteria as we outline in our paper (please refer also to Prochnow *et al.*, 2013b). The MACM/ALE analysis was based on data of about 7500 imaging studies. Therefore, far more rigid threshold criteria were appropriate and used as done also in the previous work referred to in our manuscript. This was also the case for the calculation of the difference maps.

- You wrote *"In the task, how can activation for the pre-decision and decision phases be separated despite the fixed close interval of the two phases?"*

We thank you for mentioning this important aspect and modified the description of the fMRI data analysis (p.6) based on your comment. The separation of the two phases was possible

by the event-related character of the scanning procedure which allowed performing two time-locked events with a temporal separation of 2.600 ms on average (jittered time interval) while the scanning repetition time was 2000 ms.

- You wrote *"Region of interest (ROI) analysis, paragraph 2 - "We conducted pairwise t-tests to…": Why was this uncommon analysis necessary?"*

  As we used the extracted activation estimates to explore the spatial separation and correlation with the behavioral data of these two regions of interest, we tested also if the areas would reveal different degrees of activation in the pre-decision phase and the decision phase. As we state in the paper this small volume analysis excluded such a difference.

- You wrote *"Introduction, paragraph 3, last sentence - "Recent evidence, however, suggests that gaming and ToM scenarios are based at least partly on different neural circuits": I don't get the nuance; was there an assumption that the gaming and ToM perfectly share the neural substrate?"*

  We thank you for drawing our attention to this orthographical error. We referred to gambling, not gaming scenarios.

- You wrote *"FMRT data analysis, paragraph 3 - "To ensure comparability…": I don't understand what is meant by "comparability" (i.e., with what?) or what has exactly been done here. In addition, authors should be clear about the "template" for the normalization; "Talairach space" sometimes means just a 3D brain space."*

  "Functional connectivity analyses, paragraph 1 - "above-mentioned criteria": which criteria do you mean?"

  We changed the sentences mentioned in order to be more precise (p.7).

Competing Interests: No competing interests to disclose