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Several sources of evidence point toward a link between asymmetry of prefrontal brain activity and approach–withdrawal tendencies. Here, we tested the causal nature of this link and examined if the categorization of an ambiguous approach- or withdrawal-related vocal signal can be biased by manipulating left and right frontal neural activity. We used voice morphing of affective non-verbal vocalizations to create individually tailored affectively ambiguous stimuli on an Anger–Fear continuum—two emotions that represent extremes on the approach–withdrawal dimension. We tested perception of these stimuli after 10 min of low-frequency repetitive transcranial magnetic stimulation over left or right dorsolateral prefrontal cortex or over the vertex (control), a technique that has transient inhibitory effects on the targeted brain region. As expected, ambiguous stimuli were more likely perceived as expressing Anger (approach) than Fear (withdrawal) after right prefrontal compared with left prefrontal or control stimulation. These results provide the first evidence that the manipulation of asymmetrical activity in prefrontal cortex can change the explicit categorization of ambiguous emotional signals.

INTRODUCTION

Everyday social interactions require fast interpretation of non-verbal information about emotional states and intentions of other persons. This information is often ambiguous, however, and not as straightforward to classify as are stimuli depicting prototypical expressions of basic emotions (Ekman and Friesen, 1976) commonly used in psychological research and affective neuroscience. Rather, the interpretation of an ambiguous social signal might be described as a process that involves not only the sender's but also the receiver's emotional state as shown, for example, by Niedenthal *et al.* (2001). This notion is consistent with the accounts that view the brain as a device that permanently generates expectations when dealing with sensory uncertainty (Bar, 2007). Emotional states and their underlying neural systems in a receiver might therefore bias perception of a sender's ambiguous signal by generating state–congruent expectations.

Asymmetric activity toward the left *vs* right dorsolateral prefrontal cortex (DLPFC) has been linked to approach and withdrawal tendencies, respectively, and related emotional states and traits (Harmon-Jones *et al.*, 2010). A large part of this evidence comes from studies that either correlated asymmetry of alpha power over frontal electroencephalography (EEG) sensors with participants' trait anger (approach) and fear (withdrawal; e.g. Harmon-Jones and Allen, 1998) or manipulated, for example, state anger and measured its effects on alpha asymmetry (Harmon-Jones and Sigelman, 2001). Converging evidence from functional MRI found approach motivation to be associated with increased activation in left relative to right DLPFC (Berkman and Lieberman, 2010). Asymmetric activity in this neural system, however, might also facilitate expectations about congruent states in another person. A correspondence between own emotional states and the congruent perception of other's emotional states was, for example, shown by Niedenthal *et al.* (2001). In this study, the authors induced happy or sad states by having participants watch video clips

and found effects of state on the detection of change in an emotional facial expression from happy to sad or vice versa.

Repetitive transcranial magnetic stimulation (rTMS) is a safe, non-invasive brain stimulation technique, which is able to inhibit activity of a certain brain region for a short amount of time (see e.g. Pascual-Leone *et al.*, 2000 for a short introduction to TMS). Contrary to techniques that measure neural activity like EEG and fMRI, rTMS can thus be used to study causal influences of a regions activity on behavior. This is done by transiently disrupting activity in a circumscribed brain region and measuring the effect of this manipulation on behavior, an approach often termed as 'virtual lesion'. rTMS has been successfully used to modulate frontal asymmetric activity in previous studies: inhibiting either right or left DLPFC activity has been found to change tendencies to direct attention toward or away from angry (Van Honk *et al.*, 2002a) or fearful faces (Van Honk *et al.*, 2002b). Additionally, combined rTMS and brain imaging studies suggest that asymmetric DLPFC activity might exert its influence via modulation of dopamine-dependent striatal reward circuitry (Strafella *et al.*, 2001; Ott *et al.*, 2011).

It is not clear, however, if transiently modulating asymmetric DLPFC activity in a participant would also affect his/her explicit categorization of another person's ambiguous emotional signal. In the present study, we wanted to test this possibility using rTMS.

Additionally, we wanted to test whether the above-mentioned findings related to prototypical facial expressions (Van Honk *et al.*, 2002a, b) generalize to other social signals. Recent research suggested that affective non-verbal vocalizations (ANVs) as the auditory counterpart of emotional facial expressions and a validated stimulus set of ANVs (Montreal Affective Voices) is now available for use in research on auditory affect perception (Belin *et al.*, 2008). In this stimulus set, actors were instructed to produce short emotional interjections using the vowel /a/. Whereas in speech stimuli, affective valence can be carried both by prosody and semantic content, the use of ANVs avoids these confounds and makes results more readily comparable to studies using emotional facial expressions. Most important to the present research Bestelmeyer *et al.* (2010) showed that, by using auditory morphing, ANVs are particularly useful for studying ambiguous emotional signals.

We thus morphed affective vocalizations to create anger–fear continua and identified for each participant her/his most ambiguous stimulus. We used low-frequency repetitive TMS to transiently inhibit the left or the right DLPFC and subsequently asked subjects to perform a two-alternative anger/fear categorization task on stimuli drawn from the ambiguous portion of the continua. We hypothesized that TMS-induced inhibition of right DLPFC would cause these stimuli to be more likely perceived as anger, whereas left DLPFC inhibition would bias responses toward fear.

METHODS
Participants
Eleven healthy volunteers (six female) participated (mean age = 25.8, s.d. = 7.7) and received a small financial compensation (£6/h) for their time. Four additional participants were enrolled in the study but did not complete the experiment (see below: 'Procedure'/'TMS Procedure' section). Participants reported no history of hearing impairment, had no contraindication to TMS (Rossi *et al.*, 2009) and were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). All participants were naive to the experimental hypothesis being tested. The study was advertised on the local subject pool webpage to people who had previously participated in a MRI experiment at the Centre for Cognitive Neuroimaging Glasgow. This was done to ensure that anatomical T1-weighted MRI images of each participant's head could be accessed from the local database and used to guide TMS coil positioning. We obtained written informed consent from each participant. Participants further agreed that their MRI images be used in the present study. The experiment was carried out within the School of Psychology at the University of Glasgow, and all procedures were approved by the local ethics committee.

Stimuli
ANVs were taken from the Montreal Affective Voices stimulus set (Belin *et al.*, 2008). We selected vocalizations of Anger and Fear from three different actors (one female). These stimuli were normalized for acoustic energy (root mean square). On the basis of these stimuli (digital samples of 16 bit, mono, 44.1 kHz sampling rate), we morphed angry-to-fearful continua (19 equally spaced steps between 5%/95% and 95%/5%) separately for each identity. We used auditory morphing technique implemented in STRAIGHT (Kawahara and Matsui, 2003) for stimulus manipulation using procedures similar to (Bestelmeyer *et al.*, 2010). STRAIGHT performs an instantaneous pitch-adaptive spectral smoothing to separate the voice signal into contributions arising from the glottal source (f0) and from supralaryngeal filtering (distribution of spectral peaks: formants). The voice stimuli were decomposed by STRAIGHT into three shape parameters (f0, frequency and duration) and two texture parameters (spectrotemporal density and aperiodicity), all of which can be manipulated independently from each other. In each original stimulus, we manually identified time–frequency landmarks to be put in correspondence across voices, focussing primarily on f0 and the first three formants. Morphed stimuli were then generated by resynthesis based on the interpolation (linear for time, logarithmic for f0, frequency and amplitude) of these time–frequency landmark templates. Duration of the resulting stimuli was held constant within each of three continua: 646, 788 and 950 ms, respectively.

Figure 1 displays time–frequency spectrograms of stimuli along the three continua. All stimuli were presented in stereo via Beyerdynamic headphones using the Psychophysics Toolbox Version 3 (Brainard, 1997) based on MatlabR2007b at a sound pressure level of approximately 75 dB (SPL).

Procedure
Participants attended three sessions on separate days corresponding to three sites of off-line TMS stimulation: left DLPFC, right DLPFC and vertex as a control site. Order of stimulation site was counterbalanced across participants.

Behavioral task
Before each TMS session (pretest), the point of subjective equality (PSE) of the participant was determined for each actor separately using the Method of Constant Stimuli. Participants were presented with six blocks corresponding to the three different actors in the sequence: one, two, three, one, two and three. Each block consisted of 35 trials, in which morphed stimuli were presented randomly without replacement: seven morphing steps between 5%/95% and 95%/5% anger/fear, each stimulus presented five times per block. Participants were asked to give a forced choice judgement of whether the vocalization expresses the emotion Anger or Fear. Forced choices were expressed by key presses with the index finger of the left and right hand, respectively, counterbalanced across participants to avoid possible interactions between TMS stimulation site and response hand. The proportion of Fear answers was calculated as a function of the morphing steps. Non-linear least squares regression was then used to fit a psychophysical curve to the data along the morphed continuum for each actor separately based on a cumulative logistic function of the form:

$$y = c + \frac{a}{1 + e^{\frac{x0-x}{b}}}$$

Parameterized for x/y shift by $x0/c$ and for x/y scale by b/a. The PSE was defined as the location along the morphed continuum, where the fitted curve crosses the 50% line (see Figure 2A for an example).

After 10 min of rTMS (see below), we tested participants' perception of the stimuli corresponding to the previously determined PSEs (posttest), namely, the nearest 5% step to the PSE measured on a continuous scale. Participants were presented with six blocks corresponding to different actors in the sequence: one, two, three, one, two and three. Each block consisted of 40 trials in which morphed stimuli were presented randomly without replacement: stimuli corresponding to the previously determined PSE in 24 trials and stimuli corresponding to ±10% and ±20% morphing steps around the PSE each in four trials (see Figure 2B). This was done to maximize the power to detect biases in the perception of the most ambiguous stimuli, but at the same time keeping the task meaningful for participants by additionally presenting less ambiguous stimuli.

Additionally, a six-items questionnaire was administered before and after each experimental session asking about positive and negative mood or comfort/discomfort [as in Barrett *et al.* (2004), see Supplementary Data]. The former referred to the participant's current state, the latter to the state during TMS stimulation. Each item consisted of two opposing statements (e.g. I feel very uncomfortable—I feel very comfortable, I feel very anxious/tense—I feel very calm), which were rated on a seven-point Likert scale (−3 to 3). We created an overall score by averaging over the six items, positive scores corresponding to positively valenced responses. We substracted pre-session from post-session scores, thus capturing potential changes in the participant's mood and comfort related to TMS stimulation site.

TMS procedure
Low-frequency (1 Hz) TMS was applied off-line for 10 min at 63% of stimulator output. In each participant, we quantified the threshold of stimulation intensity necessary to evoke a motor response using the
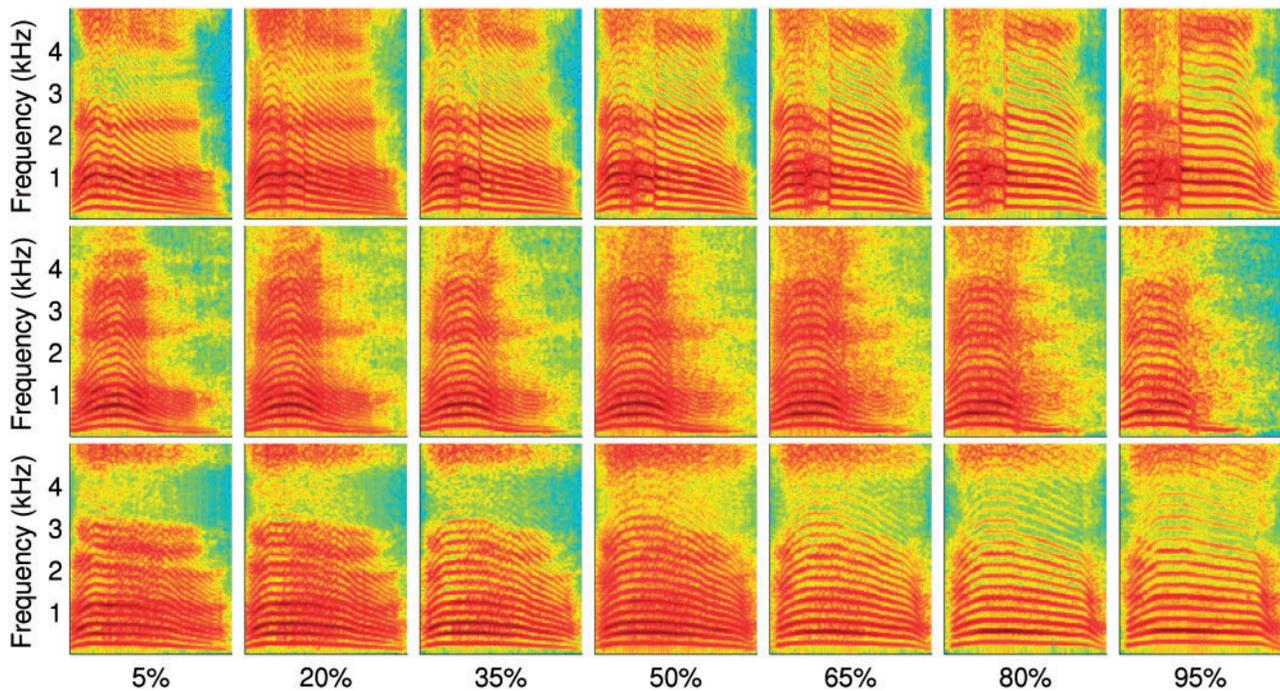
Fig. 1 Time–frequency spectrograms for the voice stimuli used in the Behavioral Task. For each of the three actors (rows) seven stimuli (columns) drawn from the morphed continuum between anger and fear are plotted.
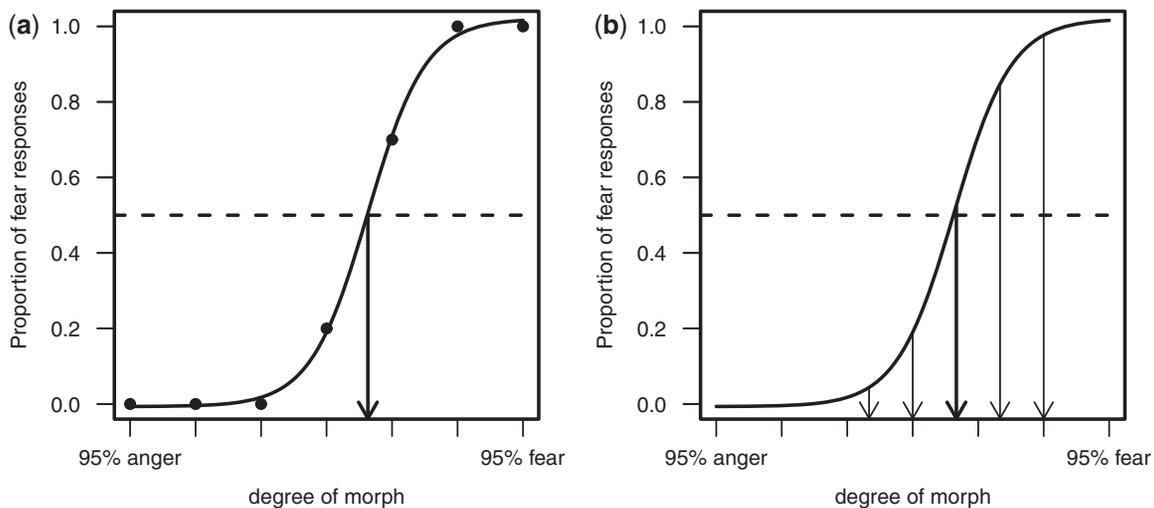
Fig. 2 (**A**) Determining the individual's PSE in the pretest. Proportion of anger–fear responses to morphed stimuli along an anger–fear continuum are plotted for one participant. The PSE was defined as the point where the fitted logistic function crosses the 50% line. (**B**) Stimulus selection for the post-test based on the previously determined PSE. See 'Procedure/Behavioral Task' section for details.

method of visualization of thumb movement (Varnava *et al.*, 2011). TMS was aborted for participants who did not feel comfortable with TMS due to peripheral nerve stimulation. Furthermore, TMS was not administered if the fixed stimulation intensity would not correspond to >100% of a participant's motor threshold (suprathreshold stimulation). Our fixed stimulation intensity corresponded to 100–121% of motor threshold in our sample (mean = 109.06, s.d. = 7.39). We chose not to set our stimulation intensity proportional to the participant's motor threshold, since we would have had to stimulate at higher and intolerable intensities in some participants to reach the same motor threshold-proportional intensity. Thus, our procedure did introduce variance in the motor threshold-proportional intensity, but at the same time ensured a high average intensity (109% of motor threshold) at tolerable stimulator output intensity.

We used frameless stereotaxy (Brainsight, http://www.rogue-research.com) to localize stimulation sites based on the individual anatomical MRI image. These were taken from a local database comprising anatomical T1-weighted MRI images of previous experiments. All scans were acquired in a 3.0 T Siemens Tim Trio scanner using standard MRI parameters. Whole-brain images consisted of 192 axial slices at a voxel resolution of 1 mm^3 and a matrix of 256×256 voxels. We determined stimulation sites using published standard coordinates of the DLPFC $[[X, Y, Z] = [\pm40, 32, 30]$ in Talairach space (Strafella *et al.*, 2001; Cho and Strafella, 2009)]. We converted those to standard MNI coordinates using a non-linear Talairach-to-MNI transformation (MATLAB function tal2mni.m from http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach), which resulted in the following coordinates: $[X, Y, Z] = [43, 37, 27]$ and $[X, Y, Z] = [-41, 36, 28]$.
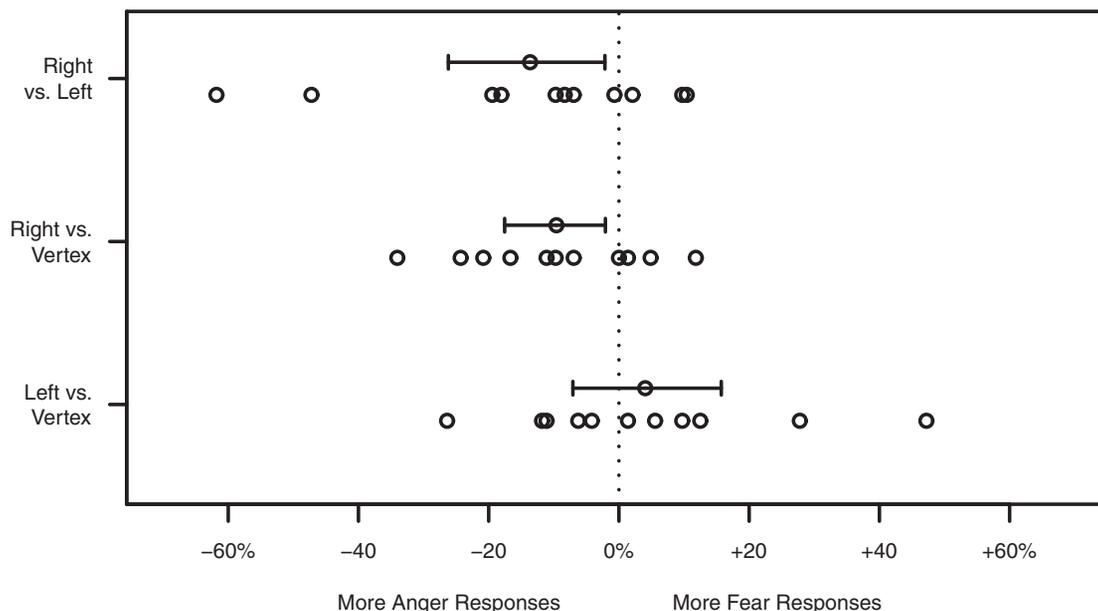
Fig. 3 Responses to the PSE stimuli in the post-test. Differences between stimulation sites are plotted for each individual alongside 95% percentile bootstrap confidence intervals of the mean difference.

Individual coordinates were then obtained by converting standard MNI coordinates to individual structural space using FLIRT affine normalization (Jenkinson and Smith, 2001) implemented in FSL (FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl/). Vertex was localized on the individual MRI based on anatomical landmarks. Coil positioning over vertex was also performed using frameless stereotaxy to keep all procedures similar across the three conditions.

The coil was held tangentially to the stimulation point with a purpose-built coil holder, the handle of the coil pointing posterior. Accurate coil position was monitored online by the Brainsight software and the experimenter corrected any deviations of over 3 mm introduced by the participant's movement.

Statistical analysis

We analyzed effects of stimulation site on the proportion of fear answers (equal to 1—proportion of anger answers) to the PSE stimuli using a one-way repeated-measures ANOVA (left, vertex, right) and a bootstrap procedure to test for its significance (Berkovits et al., 2000; Wilcox, 2012). This comprises the comparison of an observed test statistic (F) with a bootstrapped distribution of that test statistic under the null hypothesis derived from the data. To achieve this, the data from each condition were mean-centred to remove session effect. Subsequently, bootstrap samples were taken, sampling with replacement for each participant separately to account for the dependent structure of the data. For each of the 5000 bootstrap samples, we computed an F-value for the repeated-measures effect, which yields a distribution of F-values under the null hypothesis. We calculated a critical F-value at the 5% significance level, namely cutting off 5% of the highest values in the bootstrapped F-distribution, and a P-value corresponding to the proportion of bootstrapped F-values greater than the observed F-value. This procedure has been shown to control Type 1 error rate better than parametric ANOVA when normality and sphericity assumptions are violated (Berkovits et al., 2000).

We carried out our planned comparisons between stimulation sites with the analogous bootstrap-t procedure based on a dependent group t-test. A bootstrapped distribution of t-values was obtained for each comparison with 5000 re-samples. Critical t-values for the two-tailed test were calculated such that they cutoff the 2.5% highest or lowest

t-values in the bootstrapped distribution. Additionally, P-values were computed corresponding to the proportion of t-values higher or lower than the observed t-value (depending on the expected direction of effects) multiplied by 2.

Additionally, we calculated 95% percentile bootstrap confidence intervals of the mean difference between stimulation sites as a measure of effect size. We took 5000 bootstrap samples per comparison, each time sampling with replacement 11 pairs of observations and calculating the mean difference. Upper and lower confidence interval limits corresponded to the values that each cutoff 2.5% of the highest or lowest values in the resulting bootstrapped mean difference distribution.

RESULTS

Analysis of the pretest data revealed that participants' categorizations of morphed stimuli were fitted excellently by logistic psychophysical functions (mean $R^2 = 0.977$, median $R^2 = 0.990$, s.d. $= 0.039$). We found no effect of stimulation site on changes in mood as assessed with the self-report questionnaire: the one-way repeated-measures ANOVA (left, vertex, right stimulation) was non-significant [$F(2,10) = 0.75$, $P = 0.49$].

The overall effect of stimulation site on the proportion of Fear answers was marginally significant ($F_{obs} = 2.91$, $F_{crit} = 3.17$, $P = 0.065$, F_{obs}: observed F-value, F_{crit}: critical F-value derived from the bootstrap distribution, see 'Statistical analysis' section). Subsequent planned comparisons (see Figure 3) revealed significant differences between right and left stimulation [$t_{obs} = -2.00$, $t_{crit} = -1.98$, $P = 0.044$, CI (-0.02 to -0.18)] and between right and vertex stimulation [$t_{obs} = -2.32$, $t_{crit} = -2.06$, $P = 0.024$, CI (-0.02 to -0.26)], thus participants gave significantly more Anger answers after right DLPFC stimulation as compared with left DLPFC or vertex stimulation. No significant difference was found between vertex and left stimulation [$t_{obs} = -1.22$, $t_{crit} = 1.96$, $P = 0.306$, CI (0.16 to -0.07)].

DISCUSSION

To our knowledge, this is the first study to examine effects of prefrontal TMS on the explicit interpretation of emotional signals. Using auditory morphing of ANVs and psychophysical threshold

determination, we created for each individual participant stimuli on an Anger–Fear continuum that were most ambiguous to her/him. These individually tailored stimuli were again categorized by participants after off-line TMS of either right DLPFC, left DLPFC or vertex in a within-subjects design. Our results indicate that participants interpreted these ambiguous ANVs more likely as Anger after TMS-induced inhibition of the right DLPFC as compared with left DLPFC or vertex. Thus, they are partially in line with our hypothesis, which predicted differences in function of the left and right DLPFC, with relatively greater left-sided activity leading to facilitated perception of approach-related emotional signals (anger) and relatively greater right-sided activity leading to facilitated perception of withdrawal-related emotional signals (fear).

The observed effects were not due to differences in positive or negative mood or discomfort between stimulation sites. Since TMS can be slightly uncomfortable for some subjects due to peripheral nerve stimulation, the purpose of our questionnaire was to ensure that behavioral effects of stimulation site are not confounded with differences in discomfort introduced by stimulating different regions over the scalp. We acknowledge that a more detailed examination of self-reported emotional states, potentially focusing on the approach–withdrawal affect dimension, could have revealed differences, although experimental support for this is not yet conclusive. Whereas a study by Schutter *et al.*, (2001) found decreases in anxiety after right DLPFC stimulation, D'Alfonso *et al.* (2000) did not find corresponding self-reported mood differences after left/right TMS even though behavioral effects were observed. Thus, our focus in the present study was not on self-reported emotional states but on behavioral effects of stimulation. Future studies could aim at studying their interactions.

Contrary to our expectations, however, we did not find a higher amount of Fear responses after left DLPFC compared to control site inhibition. The comparison of left and right DLPFC stimulation, however, is more crucial, since stimulation via TMS is more similar in terms of the sensations on the scalp and face than that of the vertex site. We included the vertex as a control site to preclude potential effects of frontal stimulation itself, irrespective of laterality, as well as alerting effects of the clicking sounds from the coil. The null finding of the left DLPFC–vertex comparison thus does not contradict the notion of asymmetric function. It suggests, however, that effects could be driven specifically by right DLPFC function. We expect that this null finding has decreased the statistical power of our three-level bootstrap ANOVA, explaining the marginal significant effect ($P = 0.065$). We justify our subsequent planned comparisons with our strong directional hypothesis regarding the left *vs* right DLPFC difference and use a stringent two-tailed comparison despite our directional hypothesis, revealing significant differences between vertex/right DLPFC and left/right DLPFC.

This finding is in line with previous research that used TMS in the study of frontal asymmetries and generally provided more experimental support for effects of right DLPFC stimulation. Van Honk *et al.* (2002a) found increased selective attention toward angry faces after 1 Hz rTMS over the right DLPFC, but not over the left DLPFC. Correspondingly, decreased selective attention toward fearful faces was found after right DLPFC compared with placebo TMS (Van Honk *et al.*, 2002b). An effect of left DLPFC rTMS was found by the same group on reduction of memory biases toward angry faces (Van Honk and Schutter, 2006). The latter study, however, used angry and happy faces as stimuli and is thus not directly comparable to our present study. More generally, effects of right DLPFC rTMS have been further reported in research studying economic behavior. Knoch *et al.* (2006) found that disrupting right DLPFC function with rTMS lead participants to make more risky decisions in a gambling paradigm. Decision making under risk conceptually fits into the

approach–withdrawal framework, with riskier decisions corresponding to approach-related behavior and safer decision corresponding to withdrawal-related behavior. Thus, it seems that rTMS over the right DLPFC has specific effects in a wider range of behavioral domains. Based on the our design, however, we cannot determine if the effects are due to a decrease in right DLPFC function *per se* or to a change in the balance between the left and right DLPFC function.

In the present study, we used ANVs as stimuli in our emotional categorization task. We found effects concordant with results from studies using facial expressions of emotion, supporting the proposed role of ANVs as the auditory counterpart of facial expressions of emotion. Our findings indicate that effects of asymmetric DLPFC activity on emotional processing are not modality-specific. People express emotions through a variety of other means like body posture, hand gestures or prosody. Further studies should therefore test how the present results generalize to these emotional signals. Effects across different modalities would be expected, since the DLPFC is not assumed to process low-level features of a specific modality, but rather to maintain representations of higher level concepts via connections to posterior sensory areas (Curtis and D'Esposito, 2003). Activation of approach- or withdrawal-related circuitry by asymmetric DLPFC activity could influence processing and categorization in sensory areas by feedback mechanisms, as described in predictive coding literature (e.g. Bar, 2007). Based on the present study, we cannot draw conclusions about the level of processing where these biases occur. We claim, however, that our approach of studying ambiguous emotional signals can be helpful to delineate these phenomena, since feedback mechanisms and predictions should influence perception especially under sensory uncertainty. Perceptual biases like these could crucially influence the outcome of social interactions and are likely to be overlooked by researchers who focus solely on full-blown prototypical expressions of emotion.

SUPPLEMENTARY DATA

Supplementary data are available at *SCAN* online.

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