Research Article

Title: The role of medial prefrontal cortex in processing emotional self-referential information: a combined TMS/fMRI study

Authors: Nicola De Pisapia1 Guido Barchiesi2 & Jorge Jovicich1,3 & Luigi Cattaneo4

Affiliations: 1 - Department of Psychology and Cognitive Science, University of Trento, Rovereto, (TN), Italy. 2 Division of Physiological Psychology, Paris-Lodron Universität - Salzburg, Salzburg, Austria. 3 - CIMeC - Center for Mind/Brain Sciences, University of Trento, Rovereto, (TN), Italy. 4 - Department of Neurological, Biomedical and Movement Science, University of Verona, Verona, (VR), Italy

Correspondance to: Nicola De Pisapia - nicola.depisapia@unitn.it

Abstract: In this study we investigate the neural basis of emotional content in self-referential processing by using a combination of off-line repetitive Transcranial Magnetic Stimulation (rTMS) applied to the medial prefrontal cortex (mPFC) and whole-brain functional Magnetic Resonance Imaging (fMRI).We applied effective or ineffective (sham) 1-Hz rTMS to the mPFC of 14 healthy participants who immediately thereafter underwent fMRI while performing a personality attribution task to self or to others. rTMS produced an increase in the participants' reaction time (≈ 60 msec) when processing negative attributes. The neuroimaging findings indicated the involvement of a network of cortical nodes distant from those at the stimulation site; these distant nodes showed task-specific changes in blood oxygen level-dependent (BOLD) activity after effective TMS. The posterior cingulate cortex seemingly encoded the negative dimension of stimuli, but it did not differentiate between self or other. On the contrary the left angular gyrus and the left anterior temporal cortex showed changes indicating encoding of negative self-directed categorization. The mPFC region did not show effects of rTMS along the self-other dimension, but only along the affective dimension. The results indicate that the mPFC is a pivotal nodein a cortical network that supports affective referential reasoning. Therefore, a key function of mPFC seems to be related to the processing of negative attributes. In the other nodes of the network the two dimensions of self-other attribution and affective attribution are partially independent, but largely overlapping with different degrees of local specialization.

Keywords: Affective . Default mode . Transcranial magneticstimulation . Self-other . Emotions . Referential processes

INTRODUCTION

Humans have the capacity to reflect on themselves, consciously evaluating self-relevant information and attributes (Northoff et al. 2011). Studies on the neural basis of self-reflection have focused on the brain processes that individuals activate to decide whether cues appropriately describe the individual or not (van der Meer et al. 2010). Under these behavioral conditions, the anterior portion of medial prefrontal cortex (mPFC; Brodmann's Area 10) – an area in part belonging to the so-called default-mode network - is consistently found to be active (Gusnard et al. 2001; Johnson et al. 2009; Whitfield-Gabrieli et al. 2011; Qin and Northoff 2011), also in concert with subcortical areas (Northoff et al. 2009). Indirect evidence for other behavioral tasks indicates that this prefrontal node is preferentially associated with self-reflection. The mPFC has been consistently found more active in association with autobiographical memory tasks (Cabeza and St Jacques 2007), reward value processing (Kringelbach 2005), emotional processing (Etkin et al. 2011), suggesting that it has a key role in the processing of self-related internal information also in the affective domain (Kelley et al. 2002; Moran et al. 2006; Uddin et al. 2006; Molnar-Szakacs et al. 2005; Fossati et al. 2003).

An important open question concerns the specificity of the mPFC activations relative to the emotional valence of the selfdirected thought. Previous studies have found that depressed patients show hyperactivity in the mPFC during the selfreferential processing of negative words, and its activity during self-referential processing of the negative stimuli was correlated with the severity of the depressive symptoms (Yoshimura et al. 2010). Self-focus in depression has been interpreted as a process competing for brain resources due to a lack of inhibition of the default mode network, bringing to its increased activation during ruminative thoughts (Hamilton et al. 2011), and to less efficient externally-oriented cognitive processes (Lemogne et al. 2012). The mPFC area has been found to be less active in studies on mindfulness (Brewer et al. 2011), a form of mental training consisting in deliberately learning to reduce mind-wandering. While mind-wandering appears to be a cause of unhappy feelings (Killingsworth and Gilbert 2010), on the contrary mindfulness training in the long run has the net effect of changing emotional reactivity to negative events towards a more positive and benign reframing (Grecucci et al. 2015).

Another issue regarding the role of mPFC concerns the specificity of this area in processing information related just to oneself. In an extensive review of studies on self-related processing of information (Gillihan and Farah 2005), Gillihan and Farah argued that, based on previous evidence, the activation of mPFC might not be specific to the self, but rather might be a function of the amount and type of knowledge about the referent, and thus it might be also involved in processing information about others. More recently, several studies have indeed found that this area is also active when processing information about a close-other (friend) and even a distant other (the prime minister) (Yaoi et al. 2009).

Given the above-mentioned uncertainty on the function of mPFC we conducted an ad-hoc experiment to evaluate the effects of a Bvirtual lesion^ produced by repetitive transcranial magnetic stimulation (rTMS) on the mPFC on a factorial task that explored orthogonally both the negative-positive dimension and the self-other dimension. For this purpose an Boffline virtual lesion^ paradigm was used (Robertson et al. 2003; Walsh and Rushworth 1999). The effects of 1 Hz rTMS (used in the present study) on behavior are conventionally thought to be inhibitory, hence the idea of a virtual lesion. Our main hypothesis in this study was that using a factorial task that includes as orthogonal dimensions the self-other distinction and the positive-negative distinction we could assess separately these two functions. The addition of TMS over the mPFC adds the possibility to test the relation between the stimulated area and the two behavioral functions. In general, four possible outcomes are possible: (1) no effect of TMS on any of the tasks – i.e., which would indicate that none of the behavioral functions is affected by stimulation; (2–3) interaction of TMS modality (effective or ineffective) with only one of the two functions – which would indicate a main representation of that function in the stimulated cortex; (4) a 3-way interaction - which would indicate a

shared representation of both categories (referential and affective) in the stimulated cortex. Given that in the literature there are strong views over the specialization of the mPFC in one function or in the other, in this study we had no a priori hypothesison which of the fouroutcomesto expect.We instead devised our experimental paradigm to contribute to the disentanglement of the opposing but not incompatible view, with the main goal of clarifying the role of the MPFC in self-referential vs. emotional valence processing.

The effects of rTMS were assessed behaviorally. Additionally, participants were scanned with functional Magnetic Resonance Imaging (fMRI) immediately after the rTMS session, to describe the impact on the whole brain activity produced by disrupting activity in the mPFC. This design allowed us to collect behavioral and imaging data in the time-window in which the effects of effective TMS were still present, and compare them with ineffective stimulation. The considerable advantages offered by the combination of rTMS and fMRI consist in the possibility of assessing with a wholebrain measure the effects of a focal modulation of brain activity (Arfeller et al. 2013; Siebner et al. 2009). Using such condition-and-map approach, the finding of interest in areas remote from the stimulated region is that of an interaction between task-dependent BOLD activity and effectiveness (ineffective versus effective) rTMS stimulation. Such a finding indicates that the distant areas of the brain are part of a network that sub-serves the task of interest and that has been perturbed as a whole by means of rTMS.

GENERAL METHODS

Participants Fourteen right-handed participants (7 F, 7 M, age 24–37 years) took part in the experiment, which was approved by the Ethical Committee of the University of Trento. The first language of all participants was Italian. All gave written informed consent to the experiment and were screened for contraindication to TMS (Rossi et al. 2009). None had any major internal, psychiatric or neurological disorder (including mood disorders), and all were medication-free at the time of stimulation and scanning.

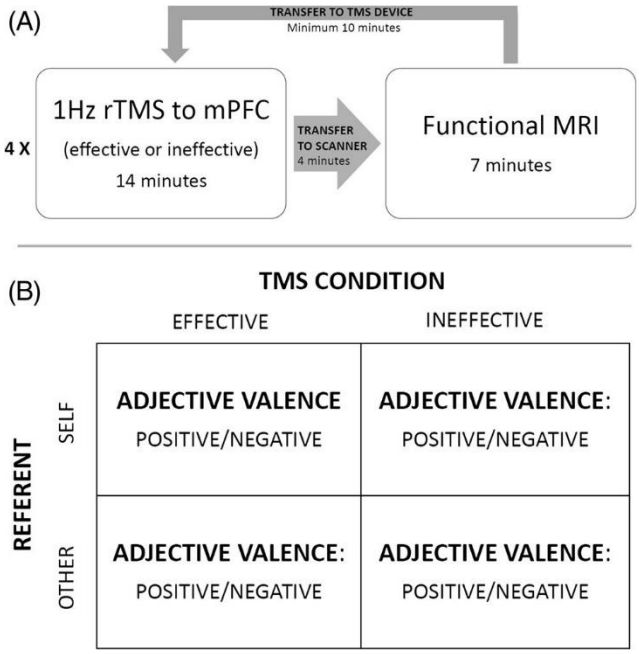

Fig. 1 *The top panel (a) shows the flow of data collection of the experiment. We applied effective or ineffective (sham, i.e., the coil was tilted) 1-Hz rTMS to the mPFC of every volunteer, who immediately thereafter underwent fMRI while performing a personality attribution task to self or to others. This sequence was repeated 4 times (2 effective and 2 ineffective, randomly alternating) for each participant. The timings of the experimental design were chosen to collect behavioral and imaging data in the time-window in which the effects of rTMS were still present. In the bottom panel (b), we show the design of the*

event related design in the fMRI scanner, factorially designed with a 2x2x2 structure. The 3 within-subject factors were: 1) the TMS condition (2 levels: effective TMS and ineffective TMS), 2) the attribution's referent (2 levels: self or other) and 3) the emotional valence of the attribute (2 levels, negative or positive). The TMS factor was blocked in each of the four TMS/fMRI runs, while the other two factors (REFERENT and VALENCE) were randomized in each trial

General design The general aim of the study was to measure the behavioral and haemodynamic effects of 1-Hz rTMS applied to the mPFC. To do so, we applied a so-called "condition-and-map" methodology (Siebner et al. 2009). In four different runs we applied rTMS to the participants' scalp for 14 min and subsequently had them to perform a series of tasks while measuring their performance and their brain's haemodynamic responses by means of fMRI. The effects of 1 Hz rTMS have been shown to last for a period equivalent to the duration of the stimulation train (R. Chen et al. 1997; W. H. Chen et al. 2003). Therefore, the rationale of the experimental design was to collect behavioral and imaging data in the time-window in which the effects of rTMS were still present.

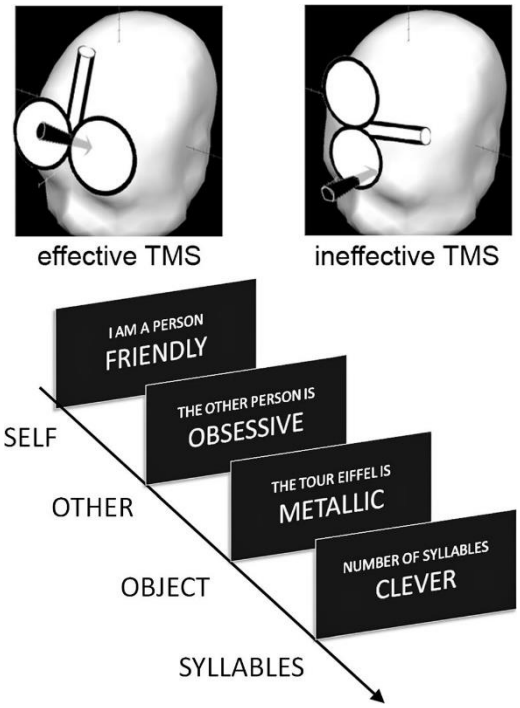

Fig. 2 *Four screenshots providing examples of each of the tasks. On the upper panel there is a representation of coil position and actual orientation in the two TMS conditions. The arrow is positioned at the point of contact of the coil with the scalp and is perpendicular to the plane of the coil. In the ineffective TMS condition the edge of the coil was in contact with the scalp and it was positioned over a region away from underlying brain tissue, i.e. the lower forehead*

The design of the experiment was event–related, factorially designed with a 2x2x2 structure. The 3 within-subjects factors were: A) the TMS condition (2 levels: effective TMS and ineffective TMS), B) the attribution's referent (2 levels: self or other) and C) the emotional valence of the attribute (2 levels, negative or positive). The first factor (hereafter referred to as TMS) was blocked in each of the four TMS/fMRI runs, while the other two factors (hereafter referred to as REFERENT and VALENCE) were randomized in each trial. Two additional tasks which served as control conditions were interleaved with the

trials of the main task. The two control conditions were a syllable counting task and a matching task of different attributes to an external non-human entity (the Eiffel tower). After rTMS, the participants were immediately transferred to the scanner. Since different trial types were randomly assigned, participants were informed at the beginning of each trial which tasks were to be performed. They had to quickly decide whether an adjective (e.g. “Selfish” or “Funny” or “French”) was (1) appropriate in describing them, (2) appropriate in describing a pre-specified close person, (3) appropriate in describing the Eiffel Tower, or (4) made of more, exactly or less than four syllables. Responses consisted in pressing one of three buttons indicating “appropriate”, “not appropriate”, “unsure” for conditions1 to3, or otherwise “less than 4 syllables”, “4 syllables”, “more than 4 syllables” for condition 4. A schematization of the four task types is shown in Fig. 2. The timing of the entire experimental procedure was as follows; (1) 14 min of TMS stimulation (effective or ineffective); (2) an average of 4 min and 5 s (standard deviation of 14 s) to transport the participants on a stretcher from the TMS room to the MRroom and start the fMRI acquisition; (3) 7 min and 12 s for the fMRI acquisition; (4) a minimum of 10 min to let the participant walk back from the MR room to the TMS room and start the stimulation. This timing, together with the randomization of the block order, ensured that (a) each effective TMS stimulation lasted during the whole fMRI acquisition of each run (given the expected effect duration of at most 14 min,as muchas the TMS stimulation), and (b) there was no carry-over effect from one TMS section to the next.

Localization of the TMS target Participants had not performed a structural MRI prior to the experimental session, therefore the localization of the mPFC was made on the basis of probabilistic systems linking the 10–20 scalp coordinates to the underlying cortical structures (Koessler et al. 2009; Okamoto and Dan 2005; Okamoto et al. 2004). It should be noted that according to these studies the anterior frontal regions are easy to target from scalp coordinates, because they present the least variability of the scalp-cortex correspondences. The cortical hot-spot for self-versus-other reflections was derived from a meta-analysis (van der Meer et al. 2010) and corresponded to the coordinates x = 0, y = 50 z = −2. By matching these coordinates with probabilistic scalp-cortex atlases, we identified the scalp position to be stimulated as a point 1 cm above the Fpz coordinate of the 10–20 system.

Magnetic stimulation A MagPro stimulator (Medtronic, DK) connected to a MCB-65 figure-of-eight coil was used. Visually assessed resting motor threshold (rMT) for the right distal upper limb was assessed individually according to standard methods (Rossini et al. 1994), namely it was defined as the intensity required to elicit a visible twitch in the fingers of the right hand in 50% of trials in a series of at least 8 consecutive trials. Biphasic TMS pulses were then applied in single trains at a frequency of 1 Hz at an intensity corresponding to 100% of the rMT. Each train had duration of 14 min (840 stimuli in total). A total of 4 trains were applied in a fully randomized order. In two trains (referred to as “effective TMS” trains) the focus of the TMS coil was systematically placed with the induced current oriented laterally, i.e. perpendicularly to the inter-hemispheric fissure. (Note that the stimulation was biphasic, therefore the current flowed in both directions at each pulse). In the other two trains (referred to as “ineffective TMS” trains) only the peripheral part of the anterior surface of the TMS coil was in contact with the skin, and it was placed over the midpoint between the two eyebrows (see top of Fig. 2). This position was chosen in order to obtain an ineffective stimulation that however produced a cutaneous sensation as unpleasant as the one produced by effective TMS. The first condition was clearly fulfilled because no cerebral tissue is found underneath the ineffective TMS target position. The second condition was made necessary because most participants reported a mild discomfort from effective TMS over such an anterior scalp region. The fulfillment of the second condition was checked post-hoc by asking participants which of the two TMS positions was less comfortable. The participants were informed that two different sites were stimulated, but were told that both stimulations were potentially efficient in stimulating the brain.

Stimuli and response modalities Verbal stimuli of the experimental conditions were selected such that each participant saw the same list of adjectives, but with a random rearrangement within the levels of the

TMS (effective vs. ineffective) x REFERENT (self vs other) factors. For the procedure to select the adjectives, please see the Supplementary material online. There were two runs after rTMS to the mPFC and two runs after ineffective TMS (order of runs was counterbalanced between subjects). Each run started with a 10 s fixation cross. Then there was a total of 18 trials for each of the four categories (72 trials in total), randomly distributed. Stimuli consisted in one of the four possible task instructions (i.e., the self, other, object or syllabic evaluation), which was presented concurrently with the relative attribute (respectively on the top and at the center of the screen, see Fig. 2). During such stimulus presentation, participants had a maximum time of 2200 msec to respond. After response, stimuli disappeared and a central fixation cross was presented for a remaining time of 2500 msec minus the response time. After this trial lasting always 2500 msec, there was a random variable time interval of 2500 msec (50% of trials), 3500 msec (33%), or 6500 msec (17%) between trials (jittering) to better estimate the event-related hemodynamic response on each trial (Ollinger et al. 2001). Therefore, the total duration of each run (72 trials) was of 432 s (7 min and 12 s). Stimuli were presented with a LCD projector (model 150) on a screen positioned at the head end of the bore. Participants viewed the screen through a mirror attached to the head coil. A button box was used to record participants' behavioral performance. Participants used their right thumb, index and middle finger on a four button MRI-safe pad. For the self, other and object tasks responses consisted of an evaluation of whether the adjective was relevant, irrelevant or neutral relative to the referent. For the syllabic task, responses consisted in judging whether the number of syllables was less, more or equal to four. Notice how errors were possible only in the syllabic task. For this task we asked participants to be quick in their judgments and respond within the given time.

Image acquisition Imaging data were acquired using a 4 T Bruker MedSpec Biospin MR scanner and a birdcage transmit, 8-channel receive head radiofrequency coil. Functional images were acquired with a single shot T2*-weighted gradient-recalled echo-planar imaging (EPI) sequence. We used 37 slices, acquired in ascending interleaved order, slightly tilted to run parallel to the calcarine sulcus, with a TR (time to repeat; the amount of time that exists between successive pulse sequences applied to the same slice) of 2200 msec (voxel resolution, 3x3x3 mm3; TE (time to echo), 33 msec; flip angle (FA), 75°; field of view (FOV), 192 × 192 mm2; slice gap, 0.4 mm). Each run consisted of 200 volumes. To correct for distortions in geometry and intensity in the EPI images, we applied distortion correction on the basis of the PSF (pointspread function) data acquired before the EPI scans (Zaitsev et al. 2004). There were five dummy scans. To be able to coregister the low-resolution functional images to a highresolution anatomical scan, we acquired a T1 weighted anatomical scan (MP-RAGE; 1x1x1 mm3; FOV, 256 × 224 mm2; 176 slices; GRAPPA acquisition with an acceleration factor of 2; TR, 2700 msec; TE, 4.18 msec; inversion time (TI), 1020 msec; 7° flip angle).

Behavioral data analysis The untrimmed reaction times (RTs) were averaged within conditions. The conditions of interest (self or other judgments) were analyzed together in a 2 × 2 × 2 (TMS x REFERENT x VALENCE) design (see above, General Design) repeated-measures ANOVA on RTs as dependent measure. A similar analysis was performed on the 2 control tasks, i.e. the syllable counting and the object tasks, in a 2 × 2 (TMS x TASK) repeated measures ANOVA. All posthoc comparisons were made with Tukey's Honestly significant difference test (HSD).

Neuroimaging data analyses Imaging data analyses were performed with the BrainVoyager Qx 2.1 software (Brain-innovation, NL). For preprocessing of the fMRI data, we performed 3D motion correction with trilinear interpolation and slice timing correction with ascending interleaved order, using the first slice as reference. Functional data were temporally high-pass filtered at 3 cycles/run length. A Gaussian kernel of 8 mm was applied to spatially smooth the images. Next, we aligned the first volume of each functional run to the high resolution anatomy. Both functional and anatomical data were transformed into Talairach space (Talairach and Tournoux 1988), using trilinear interpolation. To characterize activation differences between the various conditions we used a General Linear Model (GLM) analysis (percent signal change, no

autocorrelation correction). There were 12 predictors in total, namely self negative and positive, other negative and positive, syllabic and object task, each for both ineffective and effective TMS, each starting at stimulus presentation (task instruction plus attribute) and lasting for the maximum response time allowed (i.e., 2200 msec). Predictor time courses were convolved with a canonical hemodynamic impulse response function (2-gamma) starting at the initial fixation for each trial, also including 3D motion correction parameters. For statistical contrasts, we used random effects and FDR to correct for multiple comparisons (q(FDR)<0.05, unless otherwise reported) (Genovese et al. 2002). The contrast weights were always balanced according to the number of trials for each condition. Given the very small percentage of misses and errors (see results), these were non excluded from the analyses. In a first contrast we looked at effective TMS versus ineffective TMS, by comparing brain activity in all conditions after rTMS to mPFC versus ineffective TMS. Then, in our main contrast, to define regions of interests (ROIs) in which activity was more related to self and other processing of information, we contrasted only in the sham condition (ineffective TMS) self + other (positive and negative) versus object +syllable (q(FDR) < 0.01). ANOVA on ROI data Beta scores were used as the dependent variable in a repeated measures ANOVAs on the ROIs that were defined by the (self negative + self positive + other negative + other positive) > (object + syllable) simple contrast plus the single ROI corresponding to the cortical region targeted with rTMS. Subsequently, beta scores from each of the ROIs were analyzed separately with ANOVAs structured as 2 × 2 × 2 (TMS x REFERENT x VALENCE; see also panel (B) in Fig. 1). The possible interaction effects resulting from the ANOVAs were further explored by means of multiple pair-wise t-tests, which were corrected for multiple comparisons by using the Bonferroni methods, according to the number of repeated tests. Notice how the contrast to identify the ROIs does not lead to double dipping (Kriegeskorte et al. 2009), because it is orthogonal to the subsequent ROI analyses. In fact, the first contrast identified regions that were more active during person-related (self + other) evaluations of attributes versus the control conditions in the unstimulated brain (sham). In the ROI analyses instead we looked whether there was any effect due to the adoption of TMS, to self vs other activity differences, and to positive vs negative valence of the attributes. These three factors were not used to define the ROIs, thus no circularity is involved.

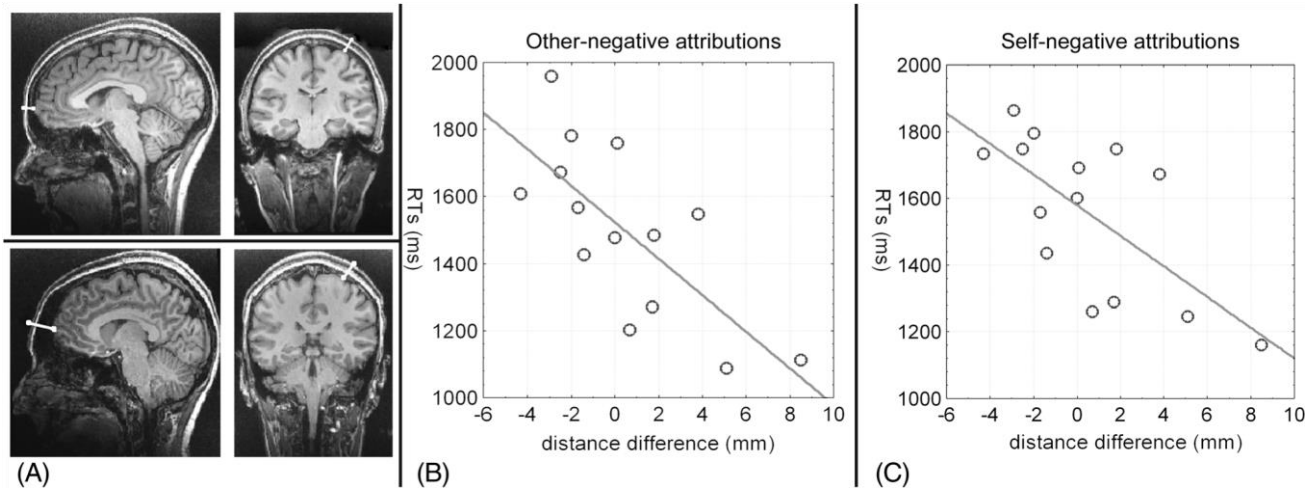

Fig. 3 *The left panel (a) shows a sagittal (x = −5) and coronal (y = −33) T1-weighted MR image of the two participants with extreme values of scalp-pial distance in mPFC (22 mm and 10 mm). The panel also shows the locations of the motor cortex (for assessing the motor thresholds) and the frontal rTMS target, as well as lines representing the calculated distances. The two plots in the figure illustrate the relation between the difference in scalp-brain distance between the motor cortex and the frontal target spot (x axis) and the reaction times to negative attributions (y axis), both other-related (panel b) and self-related (panel c). The difference between the scalp-brain distances is an index of how inappropriate the stimulation intensity was in each individual, because the TMS intensity was calculated on the motor cortex, assuming a similar scalp*

brain distance on the target cortex. More positive values indicate greater depth of the cortex in the frontal region compared to the motor cortex, ultimately indicating inefficient stimulation

RESULTS

All participants reported the stimulation to be mildly uncomfortable, but definitely tolerable. None of them abandoned the study due to the discomfort produced by TMS. All of them reported the discomfort from effective TMS and from ineffective TMS to be comparable. No other immediate or delayed undesirable side effects were reported. The mean stimulation intensity was 51% (SD: 8%) of maximum stimulator output.

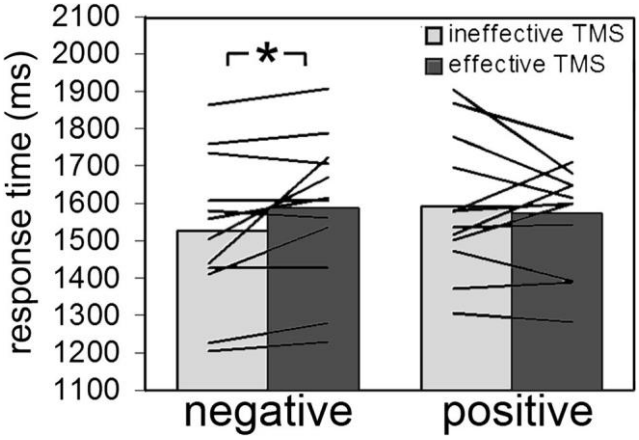

Fig. 4 *Representation of the TMSxVALENCE interaction. Single lines represent individual data. Bars represent the average value of all participants*

Scalp-brain distance assessment and post-hoc participant selection As mentioned in the methods, we did not run a first MRI session to record anatomical data, and these became available only after the experimental session was finished. When examining such anatomical images, we noticed that the distance between the modified FPz scalp coordinate and the underlying brain tissue varied considerably according to the size of the frontal sinus. Such distance varied between 10 mm to 26 mm (Fig. 3 shows the two participants with the most extreme values). The determination of the scalp-brain distance was conducted on T1 images (native images, in ACPC alignment). In both points of interest (prefrontal and motor) we performed two sequential steps. A) We first determined the most superficial cortical tissue point. This was made qualitatively on the T1 scan by looking for sudden contrast changes. B) We looked for the spot on the scalp surface that was nearest to the scalp surface by calculating geometrically the distance. This was done on a sagittal plane in the case of the prefrontal cortex and on a coronal plane in the case of the motor cortex. It is well known that the intensity of the magnetic field produced by the TMS coil decreases with the second power of the distance from the coil itself (Hallett 2007). It is therefore likely that in subjects with a greater scalp-brain distances we might not have reached the cortex with an effective magnetic field. We had used motor TMS threshold in order to individually calibrate TMS intensities, therefore the discrepancy between the scalp-brain distance on the motor cortex and the scalp-brain distance on the mPFC may have introduced an experimental bias. Therefore, for each subject we computed the difference between the scalp-brain distance on the prefrontal site and the one on the motor cortex, thus obtaining an index of inadequacy of the adopted TMS-intensity. Table 1 shows the scalp-brain distances in all subjects. We then performed an analysis of correlation between the scalp-brain distance and the RTs of the 12 behavioral conditions, i.e. the 6 conditions of self-negative, self-positive, other negative and other-positive, object and

syllable in the “effective TMS” and in the “ineffective TMS” modality. Pearson’s statistics showed a significant negative correlation between the distance difference and the RTs to self-negative attributions only for the effective TMS data ($r = -0.68$; $p = 0.007$) and other negative attributions ($r = -0.73$; $p = 0.003$) (Fig. 3 B and C). The p-values of the other correlations were all non-significant (all p-values >0.19). These results represent clear evidence that the scalp-cortex distance was likely to influence the effects of rTMS. In order to correct a posteriori for this experimental bias, we established a cut-off for exclusion of participants with too much difference in the scalp-brain distances between the motor cortex and the mPFC. Whenever the difference of scalp-cortex distances was larger than the 90th percentile of the distribution (assuming a normal distribution of the scalp-brain differences), corresponding to a measure of 4.9 mm, participants were to be excluded. Two participants out of 14 fulfilled the exclusion criterion and therefore we performed all following analyses on the group of the remaining 12 participants.

Behavioral results The percentage of misses and errors was extremely low. Concerning misses, five participants did not respond once, and one participant did not respond twice; concerning errors (possible only in the syllabic task), one participant did three errors, three participants did two errors, and one participant did one error. All the datasets of the RTs proved to be normally distributed according to the Shapiro-Wilks’ test (all p-values >0.15). The ANOVA showed two results of interest. First a significant REFERENTxVALENCE interaction ($F(1, 11) = 5.87$, $p=0.034$) was found. However, post-hoc analysis failed to show significant differences in the direct comparisons between each cell of the interaction (all p-values >0.24). We then found a TMSxVALENCE interaction ($F(1, 11)=6.99$, $p=0.023$), as is illustrated in Fig. 4. This was due, according to the HSD test, to the fact that with ineffective TMS the RTs to negative attributes were faster than those to positive attributes ($p=0.04$). This difference was not significant when effective TMS had been applied over mPFC. All other main effects and interactions were nonsignificant (all p values >0.28). The mean values of RTs are reported in Table 2.

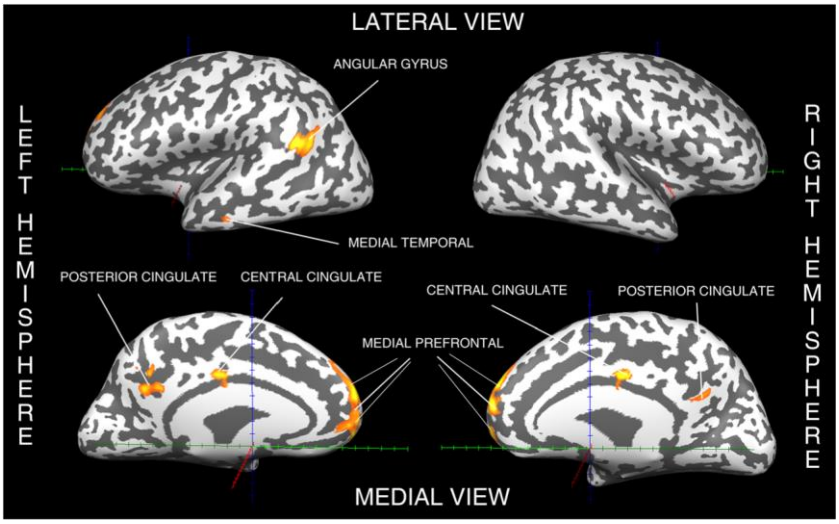

Fig. 5 *Cortical regions (inflated brain, white and grey colors refer to sulci and gyri) in which activity was more related to self and other processing of information, resulting from contrasting self + other (positive and negative) versus object +syllable (q(FDR) < 0.01) in the ineffective condition (ineffective TMS). On the left there is the left hemisphere (lateral view on the top, and medial view at the bottom), and on the right there is the right hemisphere (lateral view on the top, and medial view at the bottom). For exact coordinates of the regions, see Table 3*

ROI analyses In the first contrast in which we looked at effective TMS versus ineffective TMS, we found only one small region in the left angular gyrus (x = −39, y = −72, z = 26; n. of voxels = 9). Next, in the main contrast only in the ineffective TMS condition ([self + other] versus [object +syllable]) we identified seven ROIs. Their coordinates are indicated in Table 3 and illustrated in Fig. 5. The 3-way ANOVAs yielded varying results, which are summarized in Table 4. The experiment was designed a priori to test the effects of TMS on the referential reasoning network. Therefore, in the results of the ANOVA we focused only on the main or interactive effects involving the TMS factor. Two regions did not show any contribution of TMS to the modulation of the BOLD signal, the mPFC1 and the posterior part of the supragenual anterior cingulate cortex.

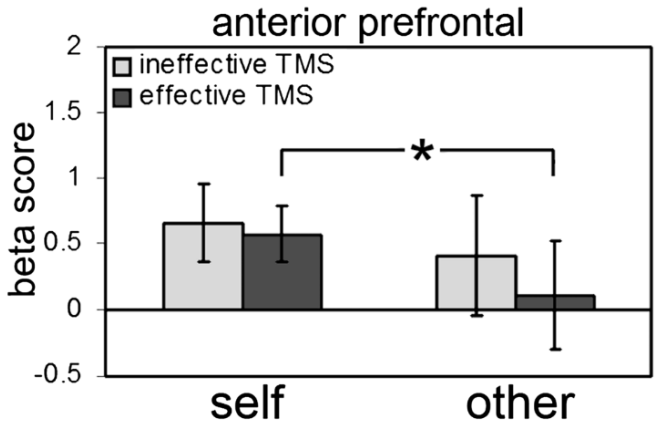

Fig. 6 *Representation of TMSxREFERENT interaction found in themPFC2 ROI in the anterior prefrontal cortex. Error bars indicate 95%confidence intervals*

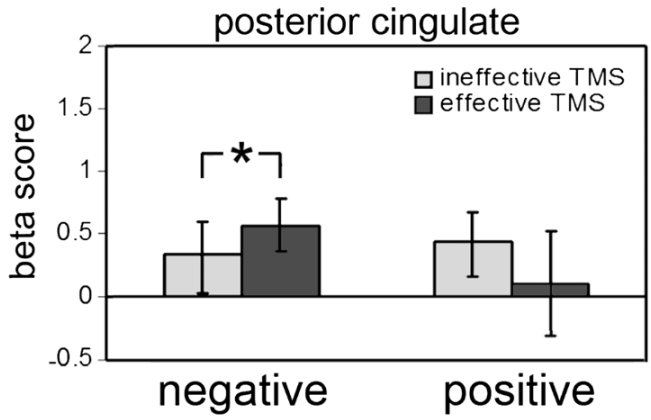

Fig. 7 *Representation of TMSxVALENCE interaction found in theposterior cingulate ROI. Error bars indicate 95% confidence intervals*

One region, the mPFC2, showed a TMSxREFERENT interaction, illustrated in Fig. 6, due to the fact that only with effective TMS the BOLD signal was reduced when performing the “other” task as compared to performing the “self” task (Bonferroni-corrected p = 0.03). The posterior cingulate cortex ROI was the only region to show a main effect of TMS, due to the fact that the beta scores were higher after effective TMS than after the ineffective TMS stimulation. The posterior cingulate cortex additionally showed a significant TMSxVALENCE interaction, illustrated in Fig. 7. The relative post-hoc comparisons indicated that effective TMS, compared to ineffective TMS, resulted in an increase in the BOLD signal associated with negative

valence (Bonferroni-corrected p = 0.01). The left angular gyrus ROI and the left temporal ROI showed a very similar pattern of activation (Fig. 8). They both produced a 3-way TMSxREFERENTxVALENCE interaction. The interaction was attributed to a selective effect of effective TMS on the SELF-NEGATIVE condition as demonstrated by separating the 3-way ANOVA in two 2 × 2 TMSxVALENCE sub-ANOVAs. Only the sub-ANOVA with data from SELF trials produced a significant 2 × 2 interaction in both the left angular gyrus ROI ($F(1, 11) = 7.32$, $p = 0.02$) and the left temporal cortex ($F(1, 11) = 9.60$, $p = 0.01$). Finally, the post-hoc analysis indicated that the interaction was in both cases due to the SELF-NEGATIVE condition, in which effective TMS produced higher beta values than ineffective TMS in both the left angular gyrus ROI (Bonferroni corrected p = 0.008) and in the left anterior temporal ROI (Bonferroni-corrected p = 0.01).

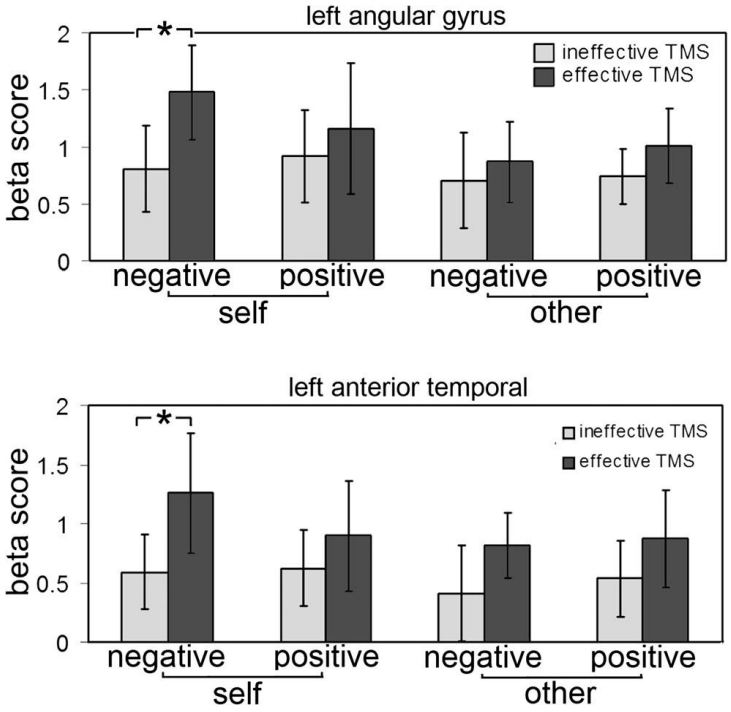

Fig. 8 *Illustration of the TMSxREFERENTxVALENCE interaction in the left angular gyrus and the left anterior temporal ROIs. Error bars denote 95% Confidence Interval (CI)*

GENERAL DISCUSSION

The principal finding of the present experiment is that 14 min of 1-Hz rTMS applied to the mPFC at adequate stimulation intensity are sufficient to produce a consistent change in participants' behavior, i.e. an increase in response times when processing negative attributes about the self or a close other. The effect is of considerable size, an average increase of about 60 msec, which was observed across participants (see Table 2 and the individual valuesinFig.4).One limitation ofthe study was that we observed that the behavioral effects of rTMS correlated significantly with the distance between the TMS coil and the brain. Such distance was considerably more variable than in other parts of the scalp because of the interposition of the frontal sinus. The data indicated that the further the coil was from the brain, the less the effect was evident on RTs. While being a limitation of the design, this post-hoc finding provided an unexpected but compelling demonstration that the impact of rTMS on behavior was specifically due to cortical stimulation rather than to non-specific effects of rTMS.

To our knowledge, this is the first study to target with rTMS such an anterior region in the medial part of the frontal lobes and correlate the effects of rTMS with a measure of referential/affective reasoning. Our

original intent in performing this study was to disambiguate the findings in the neuroimaging literature that indicate alternatively a role of the mPFC in self-other distinctions or in positive-negative distinctions (van der Meer et al. 2010). In our sample of participants, we observed effects on the affective dimension and specifically on the time needed to evaluate a negative attribute, to the self or to the others, thus providing evidence in favor of a more pronounced role of mPFC in affective coding rather than in self-other distinctions. These data fit well with neuroimaging findings in depression and rumination (Lemogne et al. 2012; Hamilton et al. 2011) that show that mood deflection is associated with stronger activity in mPFC. One intriguing possibility, also put forward in other studies (Moran et al. 2006; Beer2007), is that anterior prefrontal cortex regions involved in executive control (De Pisapia et al.2008), conscious as well as unconscious (De Pisapia2013), might have a role in emotion regulation and suppression of negative information, in particular liked to anger, fear or anxiety. Several studies describe a regulatory role for such anterior region, which acts as a top-down modulator of limbic and endocrine systems for the purpose of emotion regulation (e.g., Etkinet al. 2009). In our experiment, the ”virtual lesion” of mPFC, a key component of this supervisory mechanism, could be interpreted as inducing in the participants a stronger effort specifically in the task to evaluate whether negative adjectives (e.g., ”childish”, ”unpleasant”, “spoiled”) were appropriate in describing them or a pre-specified close person. Thus the engagement of this area appears to contribute to the control and regulation of self/other related information, but with a particular orientation or effect on negative content. In a similar vein, our findings can be interpreted also within the framework of the literature on the so-called “motivated attention”, namely the view that attention is more likely to be attracted to stimuli that have a motivational value compared to affectively neutral events. In this line of research, negative stimuli (words, images, sounds) are consistently found to induce faster responses due to the higher saliency, driven by prefrontal cortex activity (Tucker and Derryberry 1992; Lang et al. 1997). In this sense, the negative adjectives in the present experiment could be perceived as emotional and threatening, and thus triggering a heightened attention towards them. Our low frequency stimulation to mPFC might thus impair the processing advantage that is specific of negative attributes and therefore explain the significant delay in the timing to decide whether to self-attribute a negative trait or not. Within this interpretation, the increase of reaction time after effective stimulation that we found in our task can be paired to the findings of van Honk et al. 2002, in which the authors found that 1 Hz TMS over the right PFC induced a reduction in attention for fearful faces, i.e., a reversal of the motivated attention effect.

Concerning the self-other distinction, it should be kept in mind that a net behavioral effect of rTMS that is not selective for the self-other distinction does not necessarily indicate that the self-other dimension is not coded in mPFC, but only argues against an exclusive coding of self in mPFC. Such a result could in fact be due to the presence of two different neuronal populations, one coding for the self-oriented reasoning and the other coding for the hetero-oriented reasoning, with both affected by rTMS; this could account for the lack of specific effects on the referent. Also, our sample was rather small (14 participants): it is possible that with a larger population we might have obtained effects also in the self/other dimension. Further studies with larger samples of participants are required to clarify this issue.

The fMRI results indicate that the referential and the affective dimensions do not occur as two parallel and reciprocally independent categories in the brain, but rather seem to be strictly intermingled in the mPFC and in the other cortical nodes of the related network. In this respect the results of the whole-brain hemodynamic analysis are quite straightforward. Inducing a neuromodulatory input (rTMS) in one node of the network (the mPFC) on average affected activity in other nodes in the network. The majority of the BOLD changes in remote ROIs are consistent with the observed behavioral effects, i.e. they are changes related to the negative attributes, but with specific regional specializations within each ROI. The posterior cingulate cortex responded to mPFC perturbation only along the affective dimension, consistent with previous imaging studies on affective verbal stimuli (Maddock et al. 2003; Posner et al. 2009). The activity

in the left angular gyrus and temporal cortex nodes was modulated by mPFC rTMS along the self-other axis, but only for negative attributes, with a preferential encoding of the "self" dimension. This is coherent with some studies finding that self-reflection may be used in social cognition to infer the mental states of others (Mitchell et al. 2005). This is also coherent with the view that the anterior prefrontal cortex is involved in prioritizing processing of threat or anger during motivated attention situations. An impairment of this prefrontal role due to the 1 Hz rTMS could somehow allow more posterior cortical regions (left angular gyrus and temporal cortex) to show an increased activity specifically for negative adjectives. On the other end, a perfectly functioning mPFC performs the role of producing and attentional and ultimately behavioral advantage in the processing of negative stimuli, with an effect that does not remain confined to this region, but connects to several distant cortical areas, possibly biasing the elaboration of this information in the search of a faster solution to deal or cope with it. On the other end, this complex set of results should not be interpreted in the strict sense, i.e. for example that the left angular gyrus only encodes negative-self attributions. On the contrary, the key to interpret these findings is that the quality of neuromodulation in mPFC has set the tone (in this case the exclusive effects on negative attributes) to the rest of the network, which responds accordingly.

CONCLUSIONS

In conclusion, our behavioral data indicate that one main function of mPFC is that of processing affectively charged attributes, and in particular negative attributes. Also the imaging findings alone, though lacking the possibility of causal inference that is provided by the rTMS-behavioral dataset, support a specialization of the mPFC in the affective domain. Additionally, our results seem to suggest that mPFC is possibly involved in processing both self vs other relevant information, coherently with the interpretation that information processing about oneself might be instrumental to interpret information about the others (Mitchell et al. 2005). Compliance with ethical standards

Conflict of interests statement: The authors declare no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent statement: Informed consent was obtained from all individual participants included in the study.

REFERENCES

Arfeller, C., Schwarzbach, J., Ubaldi, S., Ferrari, P., Barchiesi, G., & Cattaneo, L. (2013). Whole-brain haemodynamic after-effects of 1-Hz magnetic stimulation of the posterior superior temporal cortex during action observation. Brain Topography, 26(2), 278–291. https://doi.org/10.1007/s10548-012-0239-9.

Beer, J. S. (2007). The default self: Feeling good or being right? Trends in Cognitive Sciences, 11(5), 187–189. https://doi.org/10.1016/j.tics. 2007.02.004.

Brewer, J. A., Worhunsky, P. D., Gray, J. R., Tang, Y. Y., Weber, J., & Kober, H. (2011). Meditation experience is associated with differences in default mode network activity and connectivity. Proceedings of the

National Academy of Sciences of the United States of America, 108(50), 20254–20259. https://doi.org/10.1073/ pnas.1112029108.

Cabeza, R., & St Jacques, P. (2007). Functional neuroimaging of autobiographical memory. Trends in Cognitive Sciences, 11(5), 219– 227. https://doi.org/10.1016/j.tics.2007.02.005.

Chen, R., Classen, J., Gerloff, C., Celnik, P., Wassermann, E. M., Hallett, M., & Cohen, L. G. (1997). Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology, 48(5), 1398–1403.

Chen, W. H., Mima, T., Siebner, H. R., Oga, T., Hara, H., Satow, T., et al. (2003). Low-frequency rTMS over lateral premotor cortex induces lasting changes in regional activation and functional coupling of cortical motor areas. Clin Neurophysiol, 114(9), 1628–1637, doi: S1388245703000634 [pii].

De Pisapia, N. (2013). Unconscious information processing in executive control. Frontiers in Human Neuroscience, 7, 21. https://doi.org/10. 3389/fnhum.2013.00021.

De Pisapia, N., Repovs, G., Braver, T. (2008). Computational models of attention and cognitive control. In R. Sun (Ed.), Chapter 15 of the Cambridge Handbook of Computational Psychology (pp. 422–450). Cambridge University Press. https://doi.org/10.1017/ CBO9780511816772.019

Etkin, A., Egner, T., & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. Trends in Cognitive Sciences, 15(2), 85–93. https://doi.org/10.1016/j.tics.2010.11.004.

Fossati, P., Hevenor, S. J., Graham, S. J., Grady, C., Keightley, M. L., Craik, F., et al. (2003). In search of the emotional self: an fMRI study using positive and negative emotional words. The American Journal ofPsychiatry, 160(11), 1938–1945. https://doi.org/10.1176/appi.ajp. 160.11.1938.

Genovese, C. R., Lazar, N. A., & Nichols, T. (2002). Thresholding of statistical maps in functional neuroimaging using the false discovery rate. NeuroImage, 15(4), 870–878. https://doi.org/10.1006/nimg. 2001.1037.

Gillihan, S. J., & Farah, M. J. (2005). Is self special? A critical review of evidence from experimental psychology and cognitive neuroscience. Psychological Bulletin, 131(1), 76–97. https://doi.org/10. 1037/0033-2909.131.1.76.

Grecucci, A., De Pisapia, N., Kusalagnana Thero, D., Paladino, M. P., Venuti, P., & Job, R. (2015). Baseline and strategic effects behind mindful emotion regulation: behavioral and physiological investigation. [Research Support, Non-U.S. Gov't]. PloS one, 10(1), e0116541, doi:https://doi.org/10.1371/journal.pone.0116541.

Gusnard, D. A., Akbudak, E., Shulman, G. L., & Raichle, M. E. (2001). Medial prefrontal cortex and self-referential mental activity: Relation to a default mode of brain function. Proceedings of the National Academy of Sciences of the United States of America, 98(7), 4259–4264. https://doi.org/10.1073/pnas.071043098.

Hallett, M. (2007). Transcranial magnetic stimulation: a primer. Neuron, 55(2), 187–199, doi:S0896–6273(07)00460–6 [pii]https://doi.org/ 10.1016/j.neuron.2007.06.026.

Hamilton, J. P., Furman, D. J., Chang, C., Thomason, M. E., Dennis, E., & Gotlib, I. H. (2011). Default-mode and task-positive network activity in major depressive disorder: Implications for adaptive and maladaptive rumination. Biological Psychiatry, 70(4), 327–333. https://doi.org/10.1016/j.biopsych.2011.02.003.

Johnson, M. K., Nolen-Hoeksema, S., Mitchell, K. J., & Levin, Y. (2009). Medial cortex activity, self-reflection and depression. Social Cognitive and Affective Neuroscience, 4(4), 313–327. https://doi.org/10.1093/scan/nsp022.

Kelley, W. M., Macrae, C. N., Wyland, C. L., Caglar, S., Inati, S., & Heatherton, T. F. (2002). Finding the self? An event-related fMRI study. Journal of Cognitive Neuroscience, 14(5), 785–794. https://doi.org/10.1162/08989290260138672.

Killingsworth, M. A., & Gilbert, D. T. (2010). A wandering mind is an unhappy mind. Science, 330(6006), 932. https://doi.org/10.1126/ science.1192439.

Koessler, L., Maillard, L., Benhadid, A., Vignal, J. P., Felblinger, J., Vespignani, H., & Braun, M. (2009). Automated cortical projection of EEG sensors: Anatomical correlation via the international 10-10 system. NeuroImage, 46(1), 64–72. https://doi.org/10.1016/j.

neuroimage.2009.02.006.

Kriegeskorte, N., Simmons, W. K., Bellgowan, P. S., & Baker, C. I. (2009). Circular analysis in systems neuroscience: the dangers of double dipping. Nature Neuroscience, 12(5), 535–540. https://doi.org/10.1038/nn.2303.

Kringelbach, M. L. (2005). The human orbitofrontal cortex: Linking reward to hedonic experience. Nature Reviews. Neuroscience, 6(9), 691–702. https://doi.org/10.1038/nrn1747.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1997). Motivated attention: Affect, activation, and action. Attention and Orienting: Sensory and Motivational Processes, 97, 135.

Lemogne, C., Delaveau, P., Freton, M., Guionnet, S., & Fossati, P. (2012). Medial prefrontal cortex and the self in major depression. Journal of Affective Disorders, 136(1–2), e1–e11. https://doi.org/10.1016/j.jad.2010.11.034.

Maddock, R. J., Garrett, A. S., & Buonocore, M. H. (2003). Posterior cingulate cortex activation by emotional words: fMRI evidence from a valence decision task. Human Brain Mapping, 18(1), 30– 41. https://doi.org/10.1002/hbm.10075.

Mitchell, J. P., Banaji, M. R., & Macrae, C. N. (2005). The link between social cognition and self-referential thought in the medial prefrontal cortex. Journal of Cognitive Neuroscience, 17(8), 1306–1315. https://doi.org/10.1162/0898929055002418.

Molnar-Szakacs, I., Uddin, L. Q., & Iacoboni, M. (2005). Righthemisphere motor facilitation by self-descriptive personality-trait words. The European Journal of Neuroscience, 21(7), 2000–2006. https://doi.org/10.1111/j.1460-9568.2005.04019.x.

Moran, J. M., Macrae, C. N., Heatherton, T. F., Wyland, C. L., & Kelley, W. M. (2006). Neuroanatomical evidence for distinct cognitive and affective components of self. Journal of Cognitive Neuroscience, 18(9), 1586–1594. https://doi.org/10.1162/jocn.2006.18.9.1586.

Northoff, G., Schneider, F., Rotte, M., Matthiae, C., Tempelmann, C., Wiebking, C., Bermpohl, F., Heinzel, A., Danos, P., Heinze, H. J., Bogerts, B., Walter, M., & Panksepp, J. (2009). Differential parametric modulation of self-relatedness and emotions in different brain regions. Human Brain Mapping, 30(2), 369–382. https://doi.org/10. 1002/hbm.20510.

Northoff, G., Qin, P., & Feinberg, T. E. (2011). Brain imaging of the self– conceptual, anatomical and methodological issues. Consciousness and Cognition, 20(1), 52–63. https://doi.org/10.1016/j.concog.2010.09.011.

Okamoto, M., & Dan, I. (2005). Automated cortical projection of headsurface locations for transcranial functional brain mapping. NeuroImage, 26(1), 18–28. https://doi.org/10.1016/j.neuroimage. 2005.01.018.

Okamoto, M., Dan, H., Sakamoto, K., Takeo, K., Shimizu, K., Kohno, S., Oda, I., Isobe, S., Suzuki, T., Kohyama, K., & Dan, I. (2004). Threedimensional probabilistic anatomical cranio-cerebral correlation via the international 10-20 system oriented for transcranial functional brain mapping. NeuroImage, 21(1), 99–111.

Ollinger, J. M., Corbetta, M., & Shulman, G. L. (2001). Separating processes within a trial in event-related functional MRI. NeuroImage, 13(1), 218–229. https://doi.org/10.1006/nimg.2000.0711.

Posner, J., Russell, J. A., Gerber, A., Gorman, D., Colibazzi, T., Yu, S., Wang, Z., Kangarlu, A., Zhu, H., & Peterson, B. S. (2009). The neurophysiological bases of emotion: An fMRI study of the affective circumplex using emotion-denoting words. Human Brain Mapping, 30(3), 883–895. https://doi.org/10.1002/hbm.20553.

Qin, P., & Northoff, G. (2011). How is our self related to midline regions and the default-mode network? NeuroImage, 57(3), 1221–1233. https://doi.org/10.1016/j.neuroimage.2011.05.028.

Robertson, E. M., Theoret, H., & Pascual-Leone, A. (2003). Studies in cognition: The problems solved and created by transcranial magnetic stimulation. Journal of Cognitive Neuroscience, 15(7), 948–960. https://doi.org/10.1162/089892903770007344.

Rossi, S., Hallett, M., Rossini, P. M., & Pascual-Leone, A. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clinical neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology, 120(12), 2008–2039. https://doi.org/10.1016/j.clinph.2009.08.016.

Rossini, P. M., Barker, A. T., Berardelli, A., Caramia, M. D., Caruso, G., Cracco, R. Q., Dimitrijević, M. R., Hallett, M., Katayama, Y., Lücking,

C. H., Maertens de Noordhout, A. L., Marsden, C. D., Murray, N. M. F., Rothwell, J. C., Swash, M., & Tomberg, C. (1994). Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: Basic principles and procedures for routine clinical application. Report of an

IFCN committee. Electroencephalography and Clinical

Neurophysiology, 91(2), 79–92.

Siebner, H. R., Bergmann, T. O., Bestmann, S., Massimini, M., JohansenBerg, H., Mochizuki, H., Bohning, D. E., Boorman, E. D., Groppa,

S., Miniussi, C., Pascual-Leone, A., Huber, R., Taylor, P. C. J., Ilmoniemi, R. J., de Gennaro, L., Strafella, A. P., Kähkönen, S., Klöppel, S., Frisoni, G. B., George, M. S., Hallett, M., Brandt, S. A., Rushworth, M. F., Ziemann, U., Rothwell, J. C., Ward, N., Cohen, L. G., Baudewig, J., Paus, T., Ugawa, Y., & Rossini, P. M. (2009). Consensus paper: Combining transcranial stimulation with neuroimaging. Brain Stimulation, 2(2), 58–80. https://doi.org/10. 1016/j.brs.2008.11.002.

Talairach, J., & Tournoux, P. (1988). Co-planar stereotaxic atlas of the human brain. New York: Thieme.

Tucker, D. M., & Derryberry, D. (1992). Motivated attention: Anxiety and the frontal executive functions. Cognitive and Behavioral Neurology, 5(4), 233–252.

Uddin, L. Q., Molnar-Szakacs, I., Zaidel, E., & Iacoboni, M. (2006). rTMS to the right inferior parietal lobule disrupts self-other discrimination. Social Cognitive and Affective Neuroscience, 1(1), 65–71. https://doi.org/10.1093/scan/nsl003.

van der Meer, L., Costafreda, S., Aleman, A., & David, A. S. (2010). Selfreflection and the brain: A theoretical review and meta-analysis of neuroimaging studies with implications for schizophrenia. Neuroscience and Biobehavioral Reviews, 34(6), 935–946. https:// doi.org/10.1016/j.neubiorev.2009.12.004.

van Honk, J., Schutter, D. J., d'Alfonso, A. A., Kessels, R. P., & de Haan, E. H. (2002). 1 hz rTMS over the right prefrontal cortex reduces vigilant attention to unmasked but not to masked fearful faces. Biological Psychiatry, 52(4), 312–317.

Walsh, V., & Rushworth, M. (1999). A primer of magnetic stimulation as a tool for neuropsychology. Neuropsychologia, 37(2), 125–135.

Whitfield-Gabrieli, S., Moran, J. M., Nieto-Castanon, A., Triantafyllou, C., Saxe, R., & Gabrieli, J. D. (2011). Associations and dissociations between default and self-reference networks in the human brain. NeuroImage, 55(1), 225–232. https://doi.org/10.1016/j. neuroimage.2010.11.048.

Yaoi, K., Osaka, N., & Osaka, M. (2009). Is the self special in the dorsomedial prefrontal cortex? An fMRI study. Social Neuroscience, 4(5), 455–463. https://doi.org/10.1080/ 17470910903027808.

Yoshimura, S., Okamoto, Y., Onoda, K., Matsunaga, M., Ueda, K., Suzuki, S., & ShigetoYamawaki. (2010). Rostral anterior cingulate cortex activity mediates the relationship between the depressive symptoms and the medial prefrontal cortex activity. Journal of Affective Disorders, 122(1–2), 76–85. https://doi.org/10.1016/j.jad. 2009.06.017.

Zaitsev, M., Hennig, J., & Speck, O. (2004). Point spread function mapping with parallel imaging techniques and high acceleration factors: fast, robust, and flexible method for echo-planar imaging distortion correction. Magnetic Resonance in Medicine : Official Journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine, 52(5), 1156–1166. https://doi. org/10.1002/mrm.20261.

TABLES:

Table 1 Scalp-pial distances in the 14 participants. PFC stands for prefrontal cortex

Participant	gender	Scalp-brain distance (mm)		
		Precentral gyrus	Medial PFC	Difference
1	m	15	15	0
2	m	16	14	−2
3	f	14	19	5
4	f	15	16	1
5	m	13	13	0
6	m	17	15	−2
7	f	12	14	2
8	f	14	10	−4
9	m	18	15	−3
10	m	15	19	4
11	f	13	10	−3
12	f	16	18	2
13	m	13	12	−1
14	f	18	26	8

Table 2 Mean reaction time in milliseconds (95% CI) of all participants in the experimental conditions of interest

	Ineffective TMS		Effective TMS	
	Negative	positive	Negative	positive
Self	1546 (1412:1680)	1582 (1466:1698)	1616 (1505:1727)	1546 (1467:1625)
Other	1511 (1394:1628)	1606 (1495:1717)	1563 (1442:1684)	1603 (1510:1696)
Total	1528 (1414:1642)	1594 (1488:1700)	1589 (1476:1702)	1574 (1491:1657)

Table 3 Coordinates in Talairach (26) space of the ROIs obtained with the (self negative + self positive + other negative + other positive) > (object + syllable) contrast (q(FDR) < 0.01)

Region of interest (ROI)	Peak X	Peak Y	Peak Z	t	Size (mm^3)
Medial prefontal cortex 1	−6	59	25	11.855	85,860
Medial prefrontal cortex 2	6	59	−5	12.908	63,720
Medial prefrontal cortex 3	−15	65	22	9.614	3618
Posterior supragenual anterior cingulate cortex	0	−13	34	10.716	3510
Posterior cingulate cortex	−9	−49	25	9.002	4455
Left angular gyrus	−57	−55	19	10.922	22,275
Left cerebellum	−9	−58	−38	7.535	1431
Left temporal cortex	−57	−16	−8	7.186	2754

Table 4 Results of the ANOVAs on ROI values. The F-value is given followed by the p-value. All results are intended with 11 degrees of freedom. Significant results are highlighted in bold. TMS stands for effective or ineffective transcranial magnetic stimulation; REF stands for referent (self or other); VAL stands for emotional valence (positive or negative).

	TMS	REF	VAL	TMSxREF	TMSxVAL	REFxVAL	TMSxREFxVAL
Medial prefrontal cortex 1	$F(1,11) = 0.02$; $p = 0.89$	**$F(1,11) = 16.4$; $p = 0.001$, $\eta^2 = 0.51$**	$F(1,11) = 0.25$; $p = 0.63$	$F(1,11) = 2.52$; $p = 0.14$	$F(1,11) = 0.8$; $p = 0.39$	$F(1,11) = 3.59$; $p = 0.08$	$F(1,11) = 0.17$; $p = 0.69$
Medial Prefrontal cortex 2	$F(1,11) = 0.98$; $p = 0.34$	**$F(1,11) = 7.77$; $p = 0.02$, $\eta^2 = 0.43$**	$F(1,11) = 0.89$; $p = 0.36$	**$F(1,11) = 6.24$; $p = 0.03$,, $\eta^2 = 0.36$**	$F(1,11) = 1.68$; $p = 0.22$	**$F(1,11) = 8.99$; $p = 0.01$, $\eta^2 = 0.40$**	$F(1,11) = 1.32$; $p = 0.28$
Medial Prefrontal cortex 3	$F(1,11) = 0.04$; $p = 0.68$	**$F(1,11) = 6.07$; $p = 0.03$,, $\eta^2 = 0.36$**	$F(1,11) = 0.12$; $p = 0.447$	$F(1,11) = 0.09$; $p = 0.457$	$F(1,11) = 0.17$; $p = 0.323$	$F(1,11) = 0.06$; $p = 0.527$	$F(1,11) = 0.02$; $p = 0.784$
Posterior supragenual anterior cingulate cortex	$F(1,11) = 0.38$; $p = 0.55$	**$F(1,11) = 24.75$; $p = 0.0004$, $\eta^2 = 0.72$**	$F(1,11) = 2.2$; $p = 0.17$	$F(1,11) = 0.16$; $p = 0.7$	$F(1,11) = 0.001$; $p = 0.99$	**$F(1,11) = 6.3$; $p = 0.03$, $\eta^2 = 0.46$**	$F(1,11) = 0.44$; $p = 0.52$
Posterior cingulate cortex	**$F(1,11) = 7.71$; $p = 0.02$,, $\eta^2 = 0.56$**	$F(1,11) = 0.11$; $p = 0.75$	$F(1,11) = 0.001$; $p = 0.97$	$F(1,11) = 0.61$; $p = 0.45$	**$F(1,11) = 6.55$; $p = 0.03$, $\eta^2 = 0.43$**	**$F(1,11) = 27.2$; $p = 0.0003$, $\eta^2 = 0.69$**	$F(1,11) = 0.82$; $p = 0.39$
Left angular gyrus	$F(1,11) = 3.12$; $p = 0.10$	$F(1,11) = 4.13$; $p = 0.07$	$F(1,11) = 0.02$; $p = 0.90$	$F(1,11) = 2.2$; $p = 0.17$	$F(1,11) = 0.94$; $p = 0.35$	$F(1,11) = 1.15$; $p = 0.31$	**$F(1,11) = 4.95$; $p = 0.04$, $\eta^2 = 0.35$**
Cerebellum	$F(1,11) = 0.48$; $p = 0.5$	**$F(1,11) = 6.51$; $p = 0.03$, $\eta^2 = 0.32$**	$F(1,11) = 0.31$; $p = 0.59$	$F(1,11) = 0.55$; $p = 0.47$	**$F(1,11) = 5.2$; $p = 0.04$, $\eta^2 = 0.51$**	$F(1,11) = 4.02$; $p = 0.07$	**$F(1,11) = 7.97$; $p = 0.02$,, $\eta^2 = 0.39$**
Left temporal cortex	$F(1,11) = 4.64$; $p = 0.05$	$F(1,11) = 2.44$; $p = 0.15$	$F(1,11) = 1.27$; $p = 0.28$	$F(1,11) = 0.27$; $p = 0.62$	**$F(1,11) = 4.83$; $p = 0.04$, $\eta^2 = 0.44$**	$F(1,11) = 2.11$; $p = 0.17$	**$F(1,11) = 4.86$; $p = 0.04$, $\eta^2 = 0.46$**
Target region in medial prefrontal cortex	$F(1,11) = 0.96$; $p = 0.35$	**$F(1,11) = 11.91$; $p = 0.01$ $\eta^2 = 0.38$**	$F(1,11) = 0.5$; $p = 0.49$	$F(1,11) = 1.37$; $p = 0.27$	$F(1,11) = 1.85$; $p = 0.2$	**$F(1,11) = 29.6$; $p = 0.0001$ $\eta^2 = 0.68$**	$F(1,11) = 0.18$; $p = 0.68$