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Increased Sensitivity for Happy Faces in Depressed Patients Following 15 Hz Repetitive Transcranial Magnetic Stimulation Over the Left Dorsolateral Prefrontal Cortex

Rui de Moraes Jr., Rosiberton Pereira da Cruz, and Adriana Manso Melchiades
University of Brasília

Gabriel Arantes Tiraboschi
University of São Paulo

Izabel Cristina Rodrigues da Silva and Wânia Cristina de Souza
University of Brasília

About 20% to 30% of patients diagnosed with major depressive disorder do not respond to conventional pharmacotherapy or psychotherapy. Repetitive transcranial magnetic stimulation (rTMS) has been established as an effective alternative to treat depression. The most widely used protocol and with more evidence of efficacy for major depression consists of high frequency stimulation targeting the left dorsolateral prefrontal cortex (DLPFC). However, it is unclear how and which basic psychological processes are modulated by such setup. The literature shows that the DLPFC is hyperactivated in response to facial expressions of happiness in depressed individuals, probably because they need more attentional resources to process mood-incongruent visual stimuli. The present study investigated recognition of emotional faces pre and post 15 Hz rTMS (real or sham) over the left DLPFC in participants diagnosed with major depression, and healthy controls. A double staircase design presented morphed faces and calculated the absolute threshold for the 6 basic emotions (i.e., anger, disgust, fear, happiness, sadness, and surprise). There was a significant difference only for the depression group that received rTMS: an increased sensitivity for happy faces after stimulation. We conclude that high frequency rTMS over the left DLPFC might reduce major depression typical lower bias to recognize positive valence stimuli, and hence explains the increased sensitivity for happy faces observed in the depression group.

Keywords: depression, facial expressions of emotion, dorsolateral prefrontal cortex, transcranial magnetic stimulation, neuromodulation

Facial expressions of emotion provide information on affective states and behavioral intentions (Frank & Stennett, 2001; Scherer & Scherer, 2011). In a casual conversation for instance, it is possible to know looking at a face if someone is happy or sad, excited or bored,

Rui de Moraes Jr., Rosiberton Pereira da Cruz, and Adriana Manso Melchiades, Department of Basic Psychological Processes, Institute of Psychology, University of Brasília; Gabriel Arantes Tiraboschi, Department of Psychology, University of São Paulo; Izabel Cristina Rodrigues da Silva, Faculty of Ceilândia, University of Brasília; Wânia Cristina de Souza, Department of Basic Psychological Processes, University of Brasília.

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Correspondence concerning this article should be addressed to Rui de Moraes Jr., Departamento de Processos Psicológicos Básicos, Instituto de Psicologia, Universidade de Brasília, Campus Darcy Ribeiro, ICC Sul, Sala A1-060, CEP 70910-900, Brasília DF, Brazil. E-mail: rui.moraes@unb.br

and if the words shall be interpreted literally or with irony (Heerey, 2015). Therefore, facial expressions of emotion play an important role in the development of social cognition and in the regulation of interpersonal interactions. Difficulties in their recognition compromise the individual's social adaptation and quality of life (Adolphs, 2002).

Recognition of facial expressions of emotion is altered in several clinical conditions, particularly in mental illnesses characterized by deficits in socialization, for example, schizophrenia, autism, and depression (Bistricky, Atchley, Ingram, & O'Hare, 2014; Kohler, Walker, Martin, Healey, & Moberg, 2010; Loth et al., 2018). To date, the literature has progressed mainly on the establishment of neural substrate for emotional faces processing in psychiatric disorders related to mood dysfunction (e.g., Korgaonkar et al., 2019).

In a multicenter study that used an event-related magnetic resonance paradigm, Demenescu et al. (2011) observed that facial expressions activated the amygdala and the fusiform gyrus both in healthy controls and participants diagnosed with major depressive disorder (MDD). No difference of amygdala activation was found between medicated depressed individuals and healthy controls, which leads us to consider other key structures for the understanding of MDD circuitry. Importantly, Demenescu et al. (2011) also showed that the MDD group presented hyperactivity in the dorsolateral prefrontal cortex (DLPFC) when happy faces were presented in comparison to the control group.

In cases of depression with no symptoms of remission, there is a reduction of connectivity in the left DLPFC, the ventro-lateral prefrontal cortex, the orbitofrontal region, and the left amygdala (Bezmaternykh et al., 2018; Cisler et al., 2013; Korgaonkar et al., 2019). These findings corroborate the relationship between emotional visual information processing and the physiopathology of depression (Münkler, Rothkirch, Dalati, Schmack, & Sterzer, 2015).

About 20% to 30% of people with MDD do not respond to pharmacotherapy or psychotherapy, so it is necessary to develop new therapies. Transcranial magnetic stimulation (TMS) has been consolidated as an effective alternative for MDD treatment (Fava, 2003; Gibson et al., 2010; Murphy & Byrne, 2012). TMS emits magnetic pulses of 1.5 to 3.0 T in the scalp, capable of exciting (1 Hz to 20 Hz) or inhibiting ($<$1 Hz) specific cortical areas (Janicak & Dokucu, 2015). It is a painless, noninvasive and useful procedure for both therapeutic procedures and scientific investigations associated with other behavioral and neurophysiological techniques (Becker, Shultz, & Maley, 2019; Taylor, Galvez, & Loo, 2018). When the stimulation is used for clinical purposes, the patient receives hundreds to thousands of pulses for periods of minutes to hours. This procedure is known as repetitive TMS (rTMS). The literature shows that even single session studies modulated brain activity, and consequently promoted changes in mental functions (e.g., Gay et al., 2017; Ironside, Kumar, Kang, & Pizzagalli, 2018).

Depression has been the most studied disorder using rTMS and several reviews and meta-analyses have been published on the subject (e.g., Gaynes et al., 2014; Janicak & Dokucu, 2015; Wei et al., 2017). In general, there is a rapid reduction of depressive symptoms in the first few applications, especially for drug-resistant patients (Baeken et al., 2013).

Magnetic stimulation in frontal areas, particularly in the left-brain hemisphere, reaches up to 30% remission rate for depression (Blumberger et al., 2018; Fitzgerald et al., 2011; George et al., 2010). The most widely used protocol and with more evidence of efficacy for MDD, including treatment-resistant patients, consists of high frequency stimulation over the left DLPFC (Gaynes et al., 2014; Lefaucheur et al., 2014; Slotema, Blom, Hoek, & Sommer, 2010).

Although clinical trials provide evidence on the decrease and remission of depressive symptoms, it is not clear how and which basic psychological processes are modulated by high frequency stimulation over the left DLPFC. The DLPFC has connections with the limbic system that participates in mood regulation (Barbas, 2000). It has been suggested that people with depression have a negative bias to perceive positive valence stimuli and that they need to increase attentional resources for mood-incongruent stimuli (Frodl et al., 2009; Ochsner et al., 2009), and that would be correlated to the DLPFC hyperactivation in response to facial expressions of happiness found in patients with MDD by Demenescu et al. (2011). Thus, it is possible that a therapy based on high frequency rTMS

targeting the left DLPFC could improve the sensitivity to recognize facial expressions of emotion, especially emotions of positive affective valence. To date, we have not found any study that addressed this issue.

The present study investigated the behavioral performance pre and post high-frequency rTMS over the left DLPFC in a task of emotional faces recognition in individuals diagnosed with MDD that did not respond to pharmacological treatment, and in healthy controls. The task was divided into six blocks, with one for each basic emotion (i.e., anger, disgust, fear, happiness, sadness, and surprise). The faces were morphed in order to present different emotional intensities. This technique increases the study ecological validity, whereas in social relations contexts it is necessary to identify subtle differences in emotional expressions (Münkler et al., 2015). In addition, depressed individuals present a lower performance in the recognition of low-intensity facial expressions of emotion (Surguladze et al., 2004). We implemented a double staircase psychophysical method for estimation of the absolute threshold for recognition of facial emotion in each block of the experiment. Depressed individuals were expected to perform better in the task after rTMS compared with prestimulation performance, especially for happy faces.

Method

Participants

Forty-eight participants (24 women) selected from the Psychosocial Care Center (CAPS-III) of Samambaia (Federal District, Brazil), aged between 20 and 65, and with normal or correct-to-normal vision took part in the study. The study involved a group of participants diagnosed with MDD (depression group) and a control group. All participants read and signed a statement of consent that was approved by the local research ethics committee.

Individuals of the depression group ($n = 24$) were selected by consulting active medical records of regular patients being followed up by a multiprofessional team at CAPS-III and with a cut-off point (score $\geq$20) in the Beck Depression Inventory–II (BDI-II) adapted for the Brazilian population (Gorenstein, Pang, Argimon, & Werlang, 2011). The selected patients had been using at least one class of antidepressants for more than 12 months without remission of symptoms: selective serotonin reuptake inhibitors ($n = 16$), tricyclic ($n = 4$), and atypical antidepressants ($n = 4$). Associated to antidepressants, all participants from depression group were also using a drug from the class of benzodiazepines. The patients had no history of other mental disorders, personality disorders included. The control group ($n = 24$) was composed of nonusers of psychological care services who attended CAPS-III as participants of integrative health activities offered to the community (e.g., reiki and yoga). They had no psychiatric history, did not use psychotropic drugs, and were not relatives of patients diagnosed with MDD. The control group had a maximum score of nine points in the BDI-II. The selection of the depression and control groups occurred between September 2018 and October 2018.

In both depression and control groups, participants were randomly assigned to one of two treatments: rTMS or sham. Thus, the study consisted of the following groups: (1) depression–rTMS, (2) depression–sham, (3) control–rTMS, (4) control–sham, wherein each group comprised 12 participants (six women). Participants were blinded to the experimental condition they were allocated.

To check the groups' equivalence, independent analyses of variance for the variables age and scholarity (measured as years of formal education) of the participants were implemented, with group (Depression $\times$ Control) and stimulation (rTMS $\times$ Sham) as factors. No differences were found at the significance level of 5%. The same analysis was carried out for the participants' scores in the BDI-II. As expected, the depression group had greater mean score compared with the control group, $F(1, 44) = 691.45$, $p < .001$, $\eta_p^2 = .94$ (see Table 1).

Repetitive Transcranial Magnetic Stimulation

A Neuro-MS/D device (Neurosoft, Ivanovo, Russia) delivered transcranial magnetic stimulation with a 10-mm figure-of-eight coil. The stimulation targeted the left DLPFC, located in the medial frontal gyrus and anatomically covering Brodmann's areas 9 and 46 (Brodmann, 1909). The left DLPFC was located using a marker: a 5-cm distance in the rostral direction from the parasagittal plane of the left hemi-

Table 1
Means (Standard Deviations in Parentheses) of Sample Characteristics and Differences (ANOVA) Between Clinical Group (Depression × Control) and Stimulation (rTMS × Sham) for Age, Education, and BDI-II Score

	Depression group		Control group		*F* statistic		
Variable	rTMS	Sham	rTMS	Sham	Clinical group	Stimulation	Interaction
Age (years)	35.58 (10.01)	37.08 (10.75)	35.17 (11.01)	33.58 (15.94)	.31 (*ns*)	.00 (*ns*)	.19 (*ns*)
Education (years)	13.00 (2.73)	12.92 (2.15)	13.50 (2.35)	13.67 (2.49)	.78 (*ns*)	.00 (*ns*)	.03 (*ns*)
BDI-II score	43.92 (6.24)	40.92 (7.44)	4.75 (1.54)	4.42 (1.62)	691.45 ($p < .001$)	1.34 (*ns*)	.86 (*ns*)

Note. ANOVA = analysis of variance; rTMS = repetitive transcranial magnetic stimulation; BDI-II = Beck Depression Inventory–II (adapted for the Brazilian population; see Gorenstein, Pang, Argimon, & Werlang, 2011); *ns* = not significant.

sphere's primary motor cortex. The motor cortex was identified by contraction of the left abductor pollicis brevis muscle after initial application of a 50-μV stimulus. During the stimulation, the intensity of the magnetic pulse was set at 120% of the resting motor threshold of this muscle at a frequency of 15 Hz. The session lasted 30 min, and the pulses were continuously applied at durations of 5 s, with an intertrain interval of 25 s, totaling 60 trains and 4,500 pulses delivered. The sham condition was conducted using the same coil, but with it switched off. A sound source embedded in the rTMS device reproduced a high definition recording of the equipment sound when in operation (sound intensity was controlled).

Stimuli

Twelve colored high-definition images of male faces in frontal view were extracted from the Karolinska Directed Emotional Faces (KDEF) database (Lundqvist, Flykt, & Öhman, 1998). The set comprised six pairs of images from six different KDEF actors.[1] Each pair was used in one experiment block regarding one of the basic emotions (i.e., anger, disgust, fear, happiness, sadness, and surprise). The pair of images of happy faces, for instance, contained a face image with neutral expression and another with expression of happiness; the pair of faces were morphed using Sqirlz Morph 2.1 software (Xiberpix, Solihull, United Kingdom) to produce stimuli with intermediate levels of emotional intensity in the continuous of 0% to 100% happiness, with 5% steps. This process was carried out for all pairs of faces of different emotions. The stimuli treated and used in the experiment were presented in the central visual field on a 13.3-in. screen (1080 pixels × 1920 pixels) approximately 40 cm in front of the observer. The faces' width measured approximately 7.5 degrees of visual angle.

Emotional Face Recognition Task

An adaptative task for recognition of emotional faces coded in Delphi using Community Edition 10.2 software (Embarcadero Technologies Inc., Austin, TX) was developed. The software displayed the stimuli and collected the participants' responses. The experiment comprised six blocks, one for each basic emotion, randomly presented to the participants. In each block, each trial began by pressing the spacebar on the initial screen (self-paced trials), which triggered a 500-ms presentation of a central fixation point. A face was then presented for 750 ms and followed by a response screen that displayed the question "Is the face happy?" (or sad, scared, disgusted, etc., depending on the block). The participant answered yes or no by pressing the keys *1* or *2* on a laptop keyboard. When the response was given, the initial rest screen was presented again, starting the subsequent trial.

In each block, the absolute threshold for a given basic emotion was measured by the double staircase psychophysical method (Cornsweet, 1962; Levitt, 1971). The experiment ran two series of staircased stimuli concurrently, one ascending and

[1] Original stimuli (neutral face and emotional face, respectively) selected from KDEF used in each experimental block: anger block (AM29NES and AM29ANS), disgust block (AM21NES and AM21DIS), fear block (AM08NES and AM08AFS), happiness block (AM30NES and AM30HAS), sadness block (AM13NES and AM13SAS), and surprise block (AM23NES and AM23SUS).

another descending, which initially presented faces with 15% and 85% intensity of facial emotion, respectively. Trials of ascending and descending series were randomly intermixed. The emotion intensity of each trial was calculated using the *1 up–1 down rule*. Thus, if the participant recognized the emotion of the face, the next trial decreased the emotion intensity by 5%. In the case of the participant not perceiving the emotion of the face, the next trial increased the emotion intensity by 5%. This rule allows the estimation of the 50% probability point to a "yes" response (recognition of emotion) in the psychometric function. Each block ended when the participant made 22 response reversals (i.e., when he or she stopped responding "no" and went on to say "yes" in a set of trials or vice versa). There was no limit for number of trials to interrupt each block.

Before the experiment, the participants performed a training phase, which ended when they had accomplished four response reversals. The emotional face recognition task lasted approximately 15 min.

Procedure

The experiment was performed in a single and individual session in an adapted room with sound insulation and constant illumination and temperature. The researcher remained in the room throughout the experiment. Initially, the participant was informed of the study's goals and gave written consent to take part in the experiment. The individual then received instructions on the emotional face recognition task and performed a brief training. Subsequently, the participant performed the task on a comfortable table and chair (prestimulation phase). Before the neurostimulation began, vital signs (i.e., blood pressure and pulse) were taken and motor threshold was measured. The participant then received the magnetic stimulation, which could be real (rTMS) or placebo (sham). During the stimulation, the participant sat comfortably in a reclining chair. At the end, vital signs were monitored again, and a 10 min break was taken. Last, the participant carried out the emotional face recognition task once again (poststimulation phase). The entire experimental procedure lasted approximately 85 min. Figure 1 summarizes the experiment.

Analysis

Statistical analysis aimed at checking differences in the sensitivity to recognize facial expressions of emotion before and after rTMS in all groups. Therefore, the absolute threshold for recognition of facial expressions of anger, disgust, fear, happiness, sadness, and surprise for each participant pre- and poststimulation were analyzed.

The threshold refers to the probability of 50% to recognize emotion in the faces of the experimental task performed in this study. We calculated the threshold by averaging the values of response reversal, measured as morphing level (i.e., emotional intensity in the 0% to 100%

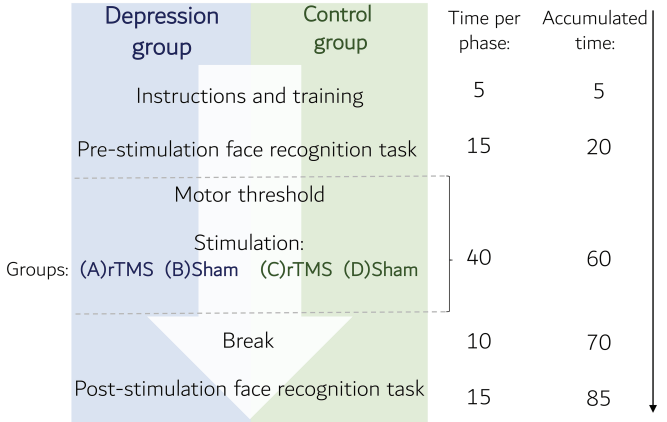

Figure 1. Sequence of the experimental procedure. See the online article for the color version of this figure.

continuous). To avoid extreme values, we did not compute the first two reversals of each block (from a total of 22). Thus, we calculated the mean from the last 20 values of response reversals of each block.

The analysis of statistical differences was conducted by running paired *t* tests.[2] Pre- and poststimulation thresholds were taken as repeated measures. Therefore, a significant effect between pre- and poststimulation conditions in the rTMS group, but not in the sham group, was considered a genuine effect of the experimental treatment. In order to control false positive results due multiple testing, we used the Benjamini-Hochberg method (Benjamini & Hochberg, 1995); the false discovery rate was set at 20%.[3]

Because we implemented an adaptive psychophysical procedure, the same analysis was conducted on the number of trials required for the participants to finish each block (i.e., to achieve 22 response reversal). Differences in the number of trials across conditions might influence threshold estimation and subject sensitivity and, hence, cause artifacts in the results (Karmali, Chaudhuri, Yi, & Merfeld, 2016; Witthoft, Sha, Winawer, & Kiani, 2018).

Results

There were six missing values (i.e., the absolute threshold, out of a total of 576) from five different participants due to file overwrite or lost data during data collection.[4] These data points were replaced by the condition median of the group in its specific experimental condition. On average, participants responded to 55.69 ($SE = 3.34$) trials per block (see Tables A1 and A2 in the Appendix for mean number of trials and standard errors for each emotion condition in all groups).

Figure 2 shows the absolute threshold mean for the six facial expressions of emotion studied, pre- and poststimulation in all groups; it also shows the raw *p* value and the Benjamini–Hochberg critical value that resulted from the comparisons between pre- and poststimulation conditions. Only the group of individuals diagnosed with MDD that received real stimulation (see Figure 2, Panel A) showed a significant difference: The absolute threshold mean and standard error for recognition of happy faces was smaller, $t(11) = 3.32$, $p = .007$ (Benjamini-Hochberg $p = .168$), in the poststimulation condition (39.03 ± 4.09) compared to the prestimulation condition (48.34 ± 4.28). No other significant difference was found when comparing the pre- and poststimulation thresholds. We also found no significant differences when conducting the same analysis for the number of trials for all emotion conditions in each group.

Discussion

The present study investigated whether the rTMS setup with more evidence of efficacy for major depression modulates recognition of facial expressions of emotion. Behavioral performance was assessed before and immediately after a single session of high frequency rTMS (real or sham) over the left DLPFC in an emotional face recognition task in patients diag-

[2] The Wilcoxon nonparametric hypothesis test was used to compare samples that had no normal distribution, as checked by the Shapiro-Wilk test ($\alpha = .05$). From the total of 48 data samples (12 per group), a nonparametric distribution was observed in four of them, which are as follows the depression group–sham: anger/prestimulation, disgust/poststimulation; control group–rTMS: anger/poststimulation; control group–sham: fear/prestimulation. Results followed those found using the paired *t* test.

[3] The Benjamini–Hochberg method controls the false discovery rate (i.e., rate of significant results that turn out to be false positives) in multiple statistical testing. In this procedure, each p-value has a rank (i; where the smallest $p = 1$) and is compared with a critical value, $(i/m)\,Q$, where m is the number of tests, and Q is the false discovery rate adopted. Significant results are given by the largest raw p value that is smaller than the critical value (i.e., $p_{raw} < (i/m)\,Q$) and by all p values smaller than it. Any p value can be converted in a Benjamini–Hochberg adjusted p value, $p_{adjusted} = p_{raw}\,(m/i)$, and statistical significance is achieved when $p_{adjusted} <$ false discovery rate. For details on the calculation, see Benjamini & Hochberg (1995). The Benjamini–Hochberg method is more powerful than Bonferroni correction, which makes it interesting for original experimental investigations. In the current study that implemented the Benjamini–Hochberg method, significant results followed those when using the Bonferroni correction to each group/sample ($\alpha = .008$), as well as those when using the uncorrected significance level (when $\alpha = .01$).

[4] Description of the missing data values by group. Depression group–rTMS: Participant 4 (thresholds of surprise/prestimulation and anger/poststimulation) and Participant 21 (threshold of surprise/poststimulation); depression group–sham: Participant 44 (threshold of anger/poststimulation) and Participant 23 (threshold of sadness/prestimulation); control group–rTMS: Participant 10 (threshold of disgust/prestimulation).

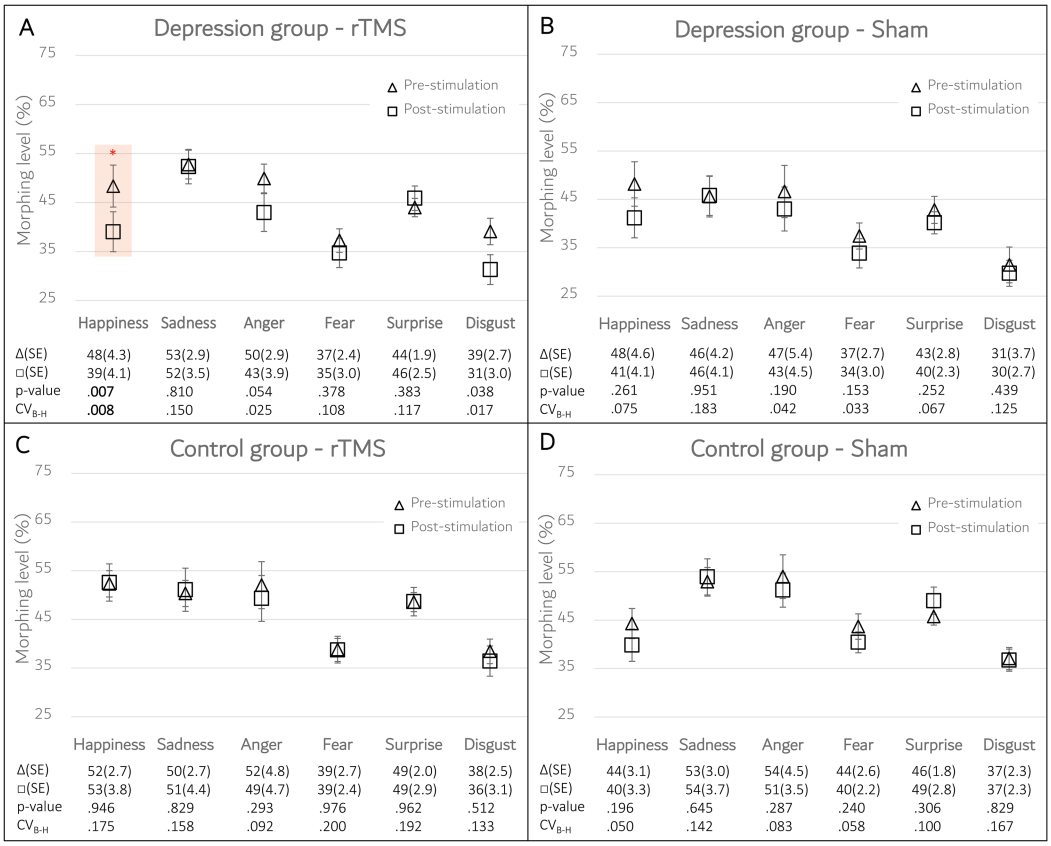

Figure 2. Absolute threshold means, measured as morphing level, for the six emotional faces pre- and poststimulation in the groups: (Panel A) depression–rTMS, (Panel B) depression–sham, (Panel C) control–rTMS, and (Panel D) control–sham. Error bars indicate standard error of the mean. Uncorrected raw p values for paired t tests between pre- and poststimulation conditions for each emotion are shown along its Benjamini–Hochberg critical value (CV_{B-H}). Benjamini–Hochberg method for multiple comparisons (false discovery rate = .2) revealed a significant difference only between pre- and poststimulation when recognizing happy faces for the depression group that received rTMS (see Panel A). See the online article for the color version of this figure.

nosed with MDD, and healthy controls. Results showed that the real stimulation increased the sensitivity to recognize facial expressions of happiness in the group composed of depressed patients. This outcome suggests that depressive individuals might benefit from high frequency rTMS in the left DLPFC by reducing a negative bias to process positive valence stimuli.

The literature shows investigations that support the idea that individuals with a clinical history of depression have impairment in processing positive valence stimuli. A study showed movies of gradual neutral-to-full-emotion morphed faces to groups of individuals diagnosed with MDD, social phobia, and healthy controls. Participants had to press a key as soon as they could perceive an emotion and then they were requested to label this emotion. Depressed participants were less sensitive to perceive happy faces compared with the social phobia and control groups (Joormann & Gotlib, 2006). Another study that used morphed faces was interested in patients with depressive episodes history but who were not currently depressed. The experiment inducted a negative mood state prior to an emotional face perception and labeling task. Results showed that currently nondepressed individuals with recurrent past

depressive episodes required greater emotional intensity to recognize happy faces, but not for angry or sad faces, compared with never-depressed control individuals (LeMoult, Joormann, Sherdell, Wright, & Gotlib, 2009). In contrast, there is evidence that MDD-related negative bias for recognizing happy faces reflects the current symptomatology rather than a stable depressive state (Münkler et al., 2015). Thus, it is still unclear if this negative bias for facial expression of happiness serves as (1) an identification of stable-vulnerability trait in individuals at risk or (2) a behavioral marker confined to the depressive episode. Last, a study that used an affective priming paradigm with prolonged presentation of emotional faces also adds evidence toward an impairment in processing positive affect valence stimuli in individuals with MDD (LeMoult, Yoon, & Joormann, 2012). Importantly, an impairment to perceive, recognize, or identify positive stimuli might deepen impairments in social interaction and thus intensify depressive symptoms. The descriptive data of the present study shows that the control group that received rTMS had a higher mean threshold (i.e., lower sensitivity) for recognizing happy faces compared with mean threshold of (1) depression group that received rTMS and (2) depression group that received sham stimulation. However, none of these comparisons were statistically significant (additional analysis using paired *t* test: $\alpha = 5\%$). We believe that such output is due the sample size. It is worth noting that descriptive data from control group that received sham stimulation showed lower threshold (i.e., higher sensitivity) compared with depression groups to recognize happy faces in the prestimulation condition.

Besides a negative bias to process positive affect valence stimuli, the literature points out that depressed individuals also show a positive bias to process mood-congruent stimuli (e.g., sad faces). This effect was found both in individuals with MDD (Gollan, Pane, McCloskey, & Coccaro, 2008) and those with nonclinical depressive symptoms (Nakamura, Takizawa, & Shimoyama, 2018). For a review on the issue, see Bourke, Douglas, and Porter (2010). All in all, MDD is characterized for a mood-congruent processing bias. Here, a bias of perception was observed by assessing sensitivity to facial expressions of emotions before and after neuromodulation. However, this bias goes beyond perception and encompasses other cognitive domains (e.g., attention, memory, and judgment) and is a framework for general cognitive theories. Beck (1967) argued that individuals with MDD see the world, themselves and the others through a negative lens, namely schemata. A schemata consists of stable cognitive patterns, which includes biased mood-congruent cognitive processing.

A systematic review of neuroimaging findings supports a mood-congruent bias in the face network to process facial expressions of emotion in MDD individuals (Stuhrmann, Suslow, & Dannlowski, 2011). In short, hyperactivation and hypoactivation were found for negative and positive valence stimuli presentation, respectively, in the amygdala, insula, parahippocampal gyrus, fusiform face area, and putamen. However, prefrontal areas showed inconsistent results, probably due differences in experimental designs and sample characteristics.

A specific neurophysiological marker was found in a prefrontal area for MDD patients during a facial expression task in the investigation of Demenescu et al. (2011). They conducted a multicenter fMRI study in a sample composed of healthy controls ($n = 56$) and patients with MDD ($n = 59$), anxiety disorder ($n = 57$), and depression-anxiety comorbidity ($n = 66$). An event-related paradigm experiment showed each face image for 2.5 s followed by an interstimulus interval that varied between 0.5–1.5 s. The only MDD-specific functional pattern was hyperactivation in response to happy faces in the right DLPFC. It was suggested that since depressed individuals have a negative bias to recognize positive valence stimuli, they need to increase attentional resources for mood-incongruent stimuli and this would be correlated to a stronger activation of the DLPFC (Demenescu et al., 2011; Frodl et al., 2009; Ochsner et al., 2009).

Our study also supports the idea that the DLPFC plays a key role in the facial expressions network impaired in MDD. We provided a causal relation between perception of facial expression of happiness, a mood-incongruent stimulus for MDD, and the DLPFC. However, unlike Demenescu et al. (2011) that provides a link between the perception of happy faces and the right DLPFC, we showed this link in the left DLPFC. The choice for targeting the left side considered the literature on rTMS protocols for major depression. The most effective rTMS

setup for MDD consists of high frequency stimulation over the left DLPFC (Gaynes et al., 2014; Lefaucheur et al., 2014; Slotema et al., 2010). We suggest that high frequency rTMS over the left DLPFC might reduce a typical lower bias to perceive positive valence stimuli found in depression, and hence explains the increased sensitivity for happy faces observed in the depression group following stimulation.

The increased sensitivity for happy faces observed following rTMS can also be discussed in terms of functional brain asymmetry. Studies show laterality effects in a variety of face processing tasks, for example, spatial frequency sensitivity, configural/featural encoding, and emotional processing (e.g., de Moraes, Faubert, Vasques, Cravo, & Fukusima, 2017; Renzi et al., 2013; Torro-Alves, Fukusima, & Aznar-Casanova, 2008). According to the valence hypothesis proposed by Davidson (1995), the left hemisphere is dominant for positive emotions processing (happiness and surprise) and the right hemispheres is dominant for negative emotions processing (anger, disgust, fear, and sadness). It might be possible that the left hemisphere processes mainly happy faces, which presents a negative bias in MDD, and that would be restored by rTMS therapy as implemented in this study. On the other hand, the right hemisphere prioritizes negative valence stimuli (e.g., sad or fearful faces), and hence would have a positive bias in MDD. The study of Notzon, Steinberg, Zwanzger, and Junghöfer (2018) supports a lateralization in the right hemisphere. They recorded whole-head magnetoencephalography while healthy participants viewed neutral and fearful faces in two moments: before and after rTMS in the right DLPFC. Right occipital and temporal activations were reduced for fearful faces after excitatory stimulation and increased after inhibitory stimulation. However, the valence hypothesis is not a consensus and there is evidence against lateralized emotional processing of faces in the DLPFC using TMS (Ferrari, Gamond, Gallucci, Vecchi, & Cattaneo, 2017). Future investigations might implement experimental designs with stimulation conditions in both brain hemispheres in order to assess laterality effects.

The present study should be viewed in the light of some limitations and strengths. One limitation concerns the difficulty to control patients' medication regarding drug class and dose. Because our participants were selected from CAPS-III, drug administration was already established. Only treatment-resistant patients were selected. Our study is relevant since it adds evidence to the perceptual gains of rTMS in patients who do not respond to conventional pharmacotherapy. A second limitation refers to a carry-over effect. Participants can perform better at a perception task if it was carried out previously, especially in a short time window. However, a significant effect due the experimental treatment consistent with the literature was found. For future investigations, we suggest pre- and poststimulation measures separated by a much longer time window in a full clinical protocol in order to assess accumulated and plasticity-related changes in recognition of facial expressions. One last limitation refers to the sham condition. An optimal sham condition would mimic the cutaneous sensation and muscular discomfort of rTMS perceived in prefrontal areas (Arana et al., 2008). However, a sham rTMS coil was not available. The same coil for active rTMS was used. Instead of tilting the coil, it was switched off and an rTMS-like ambient sound was reproduced to avoid residual brain stimulation. A recent work warns that current sham TMS approaches are not full control conditions and that they must be viewed as complementary control strategies (Duecker & Sack, 2015). Besides a sham condition, our study had a heathy control group and each participant was himself a control when the pre- and poststimulation measures are considered.

It is important to highlight that in-house software was built to implement an adaptative psychophysical method. It enables a fast and accurate measure of one's sensitivity to emotional faces very suitable for research and clinics. In addition, the current work also discussed from the basic perspective a cognitive bias that is closely related and underlies deficits in social skills and interpersonal interactions in depressed individuals. Our findings contribute to the progress of rTMS interventions in major depression and might help expand discussions regarding the use of rTMS as a therapeutic possibility, seeking to benefit treatment-resistant patients. However, further investigations are needed. This initial experimental study might be followed by a clinical trial study with a larger sample and increased statistical power in an *n*-sessions complete protocol for appropriate

discussion on clinical efficacy of rTMS. Clinical trials could also answer a question opened by the present study: could it be possible that visual processing of facial expressions, as measured by absolute thresholds, is a potential marker of rTMS treatment response?

To summarize, the current work provides new evidence on how rTMS modulates visual perception in major depression. We showed that high frequency rTMS in the left DLPFC increases sensitivity for mood-incongruent stimuli in depressed individuals (i.e., happy faces). We also added a piece to understand the puzzle of MDD physiopathology related to emotion processing by establishing a causal relationship between the left DLPFC and recognition of emotional faces. We conclude that individuals diagnosed with MDD might benefit from therapy based on high frequency rTMS in the left DLPFC by reducing a negative bias to process positive valence stimuli. This is of considerable importance in social interactions in depressed individuals.

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(*Appendix follows*)

Appendix

Table A1
Mean Number of Trials (Standard Errors in Parentheses) for Each Condition of Facial Expression of Emotion (Pre- and Poststimulation) for Both Depression Groups (rTMS and Sham)

	rTMS		Sham	
Emotion	Prestimulation	Poststimulation	Prestimulation	Poststimulation
Happiness	60.3 (6.1)	59.3 (6.4)	56.5 (2.4)	55.8 (2.6)
Sadness	65.8 (5.0)	57.7 (4.4)	54.8 (2.4)	57.7 (3.0)
Anger	59.0 (1.8)	58.3 (3.1)	65.6 (8.8)	57.2 (2.5)
Fear	52.2 (2.4)	57.5 (2.8)	54.8 (2.6)	57.3 (3.0)
Surprise	56.4 (2.1)	54.6 (2.7)	57.4 (5.8)	54.8 (2.9)
Disgust	56.2 (2.9)	62.5 (9.6)	55.2 (2.9)	55.7 (2.6)
Mean	58.3 (3.4)	58.3 (4.8)	57.4 (4.1)	56.4 (2.8)

Note. rTMS = repetitive transcranial magnetic stimulation.

Table A2
Mean Number of Trials (Standard Errors in Parentheses) for Each Condition of Facial Expression of Emotion (Pre- and Poststimulation) for Both Control Groups (rTMS and Sham)

	rTMS		Sham	
Emotion	Prestimulation	Poststimulation	Prestimulation	Poststimulation
Happiness	58.5 (4.2)	53.7 (2.4)	56.3 (2.8)	53.8 (2.0)
Sadness	56.8 (2.1)	59.3 (4.2)	55.2 (2.4)	51.1 (1.7)
Anger	56.3 (3.0)	57.0 (2.2)	61.6 (5.4)	53.4 (1.5)
Fear	54.3 (1.8)	50.1 (1.5)	51.3 (3.1)	51.6 (1.6)
Surprise	53.1 (2.6)	49.7 (2.3)	53.8 (2.2)	53.2 (2.9)
Disgust	52.3 (2.0)	47.4 (1.4)	49.6 (1.4)	52.1 (1.7)
Mean	55.2 (2.6)	52.8 (2.3)	54.6 (2.9)	52.4 (1.9)

Note. rTMS = repetitive transcranial magnetic stimulation.

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