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PSYCHIATRY AND PRECLINICAL PSYCHIATRIC STUDIES - ORIGINAL ARTICLE

Effects of prefrontal rTMS on autonomic reactions to affective pictures

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Abstract Repetitive transcranial magnetic stimulation (rTMS) can modulate the excitability of stimulated cortical areas, such as prefrontal areas involved in emotion regulation. Low frequency (LF) rTMS is expected to have inhibitory effects on prefrontal regions, and thereby should disinhibit limbic activity, resulting in enhanced emotional and autonomic reactions. For high frequency (HF) rTMS, the opposite pattern might be assumed. The objective of this study was to determine the effects of different rTMS frequencies applied to the right dlPFC on autonomic functions and on emotional perception. In a crossover design, two groups of 20 healthy young women were either stimulated with one session of LF rTMS (1 Hz) or one session of HF rTMS (10 Hz), compared to sham stimulation. We assessed phasic cardiac responses (PCR), skin conductance reactions (SCR), and emotional appraisal of emotional pictures as well as recognition memory after each rTMS application. After LF rTMS, PCR (heart rate deceleration) during presentation of pictures with negative and neutral valence was significantly increased compared to the presentation of positive pictures. In contrast, the modulatory effect of picture valence and arousal on the cardiac orienting response was absent after HF rTMS. Our results suggest that frontal LF rTMS indirectly activates the ANS via inhibition of the right dlPFC activity, likely by enhancing the sensory processing or attention to aversive and neutral stimuli.

Keywords Repetitive transcranial magnetic stimulation · rTMS · dlPFC · Autonomic nervous system · Heart rate · Skin conductance

Introduction

Emotion regulation is fundamental for human beings to adapt to the environment. There are a number of emotion regulation strategies, including emotion suppression, reappraisal (Gross 2002), distraction (Tracey et al. 2002), and detachment (Beauregard et al. 2001). Regulation is thought to result from an intricate interplay between automatic bottom-up appraisals of a given stimulus in ventral emotion processing regions such as the amygdala, and top-down stimulus appraisal, primarily by dorsal frontal control regions, such as dorsolateral prefrontal cortex (dlPFC) and the dorsomedial prefrontal cortex (Ochsner and Gross 2007; Phillips et al. 2003a). These frontal and cingulate areas are part of fronto-parietal cognitive-linguistic control networks implicated in effortful reappraisal by cognitively reframing the affective meaning of a negative stimulus in more neutral terms (Ochsner and Gross 2007). Dysfunctional interactions of dorsal–ventral circuitries are hypothesized to be involved in altered

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emotion perception in psychiatric conditions (Phillips et al. 2003b). Studies in non-psychiatric participants have confirmed that cognitive reappraisal recruits the dlPFC and dorsomedial PFC, resulting in the down-regulation of amygdala reactivity (Ochsner et al. 2012). On the other hand, amygdala activity is positively associated with memory for emotional contents (McGaugh 2006).

The amygdala is a core region involved in the regulation of the autonomic nervous system (ANS) via the brainstem and the thalamus and thus controls autonomic reactions to emotional stimuli including heart rate and skin conductance (LeDoux 2000). The amygdala is associated with a network of regions including anterior cingulate cortex, insula and periaqueductal grey matter (PAG), which mediates cardiovascular reactions to psychological stressors (Gianaros et al. 2012; Gray et al. 2009). The clinical manifestations in psychiatric patients suggest that there is a link between cortical structures and the ANS. A recent meta-analysis found that a network of brain regions comprising the amygdala, right anterior and left posterior insula and midcingulate cortices are consistently associated with peripheral markers of ANS activity (Beissner et al. 2013). The involvement of the amygdala in parasympathetic regulation is an important finding that may reflect the need for balancing both increased sympathetic and decreased parasympathetic outflow in response to aversive stimuli (Beissner et al. 2013).

In various psychiatric disorders associated with dysfunctional emotion regulation, previous studies have demonstrated hypoactivity of prefrontal brain regions, as well as hyperactivity of the amygdala (Altshuler et al. 2005; Zhong et al. 2011). For instance, impaired emotion regulation was reported in anxiety (Goldin et al. 2009; Hermann et al. 2009), borderline personality disorder (Schulze et al. 2011) and depression (Johnstone et al. 2007; Kanske et al. 2012). Furthermore, there is evidence for differences between the hemispheres in processing emotional valence: Positive emotions seem to be related to increased dlPFC activity in the left hemisphere (Herrington et al. 2005), whereas in clinical depression, hypoactivity of the left dlPFC is associated with negative emotional judgment while right dlPFC hyperactivity is linked to attentional modulation (Grimm et al. 2008).

Repetitive transcranial magnetic stimulation (rTMS) is a neurophysiological tool to modulate cortical excitability. It is widely used in therapeutic studies of neuropsychiatric disorders (Lefaucheur et al. 2014). Low frequency (LF) rTMS reduces cortical excitability (Chen et al. 1997), whereas high frequency (HF) rTMS leads to the opposite effect (Pascual-Leone et al. 1994). Repetitive TMS can also modulate activity of deeper brain structures via intra- and intercortical connections (Stagg et al. 2010). In the prefrontal-limbic circuitry recruited in emotion regulation, LF rTMS is expected to have an inhibitory effect on the dlPFC, and thereby should disinhibit limbic activity, resulting in enhanced emotional reactions. For HF stimulation the opposite pattern might be assumed. However, rTMS studies on emotion processing used heterogeneous experimental methods and reported inconsistent results, depending on the underlying clinical conditions. A single application of HF rTMS over the right dlPFC increased levels of attention towards negative emotional faces in healthy women, a finding that was interpreted as an rTMS-induced functional disruption of fronto-limbic-circuitry (De Raedt et al. 2010; Leyman et al. 2009; Vanderhasselt et al. 2011). On the other hand, it might also be interpreted as a sensitization of the fronto-limbic circuitry to negative emotions. Furthermore, LF rTMS over the right dlPFC in healthy subjects decreased anxiety (Schutter et al. 2001), and improved depressive symptoms in patients (Klein et al. 1999).

Because the dlPFC is also involved in the regulation of the ANS, it could be assumed that rTMS-induced modulation of neural activity in the dlPFC affects autonomic peripheral reactions to emotionally arousing pictures, e.g., changes heart rate and skin conductance reactivity. Studies on frontal rTMS effects on cardiovascular reactions reported that the LF rTMS has an influence on cardiac rhythm (Cabrerizo et al. 2014). LF rTMS may induce an increase in vasomotor reactivity, and, in addition, changes in heart rate variability (HRV), which suggest a possible ANS modulation (Vernieri et al. 2014). However, the data on rTMS influence on ANS functioning are heterogeneous and based only on small sample sizes (Schestatsky et al. 2013).

The aim of the present study was to investigate the effect of two different rTMS frequencies over the right dlPFC to systematically compare inhibitory and excitatory rTMS on heart rate and skin conductance as ANS activity markers during the processing of emotional stimuli in healthy female participants. To avoid gender effects on emotion processing (Bradley et al. 2001; Domes et al. 2010; Whittle et al. 2011), only women were included in the study.

We hypothesized that the (inhibitory) LF rTMS of the right dlPFC leads to enhanced activity of the amygdala as a part of the ANS, which is expressed in increased autonomic outflow, such as increased cardiac and electrodermal reactions during the emotional perception (presentation of pictures with emotional contents). Furthermore, the induction of enhanced amygdala activity via the LF rTMS should increase the emotional saliency of different emotional stimulation valences. Additionally, increased saliency for emotional pictures during memory encoding should influence attention selectivity, which may lead to more distinctive encoding and to an increased memory

performance in a later recall (Ochsner 2000). We expected contrary effects for the HF rTMS, which facilitates the activity of the dlPFC and inhibits the amygdala activity and thus decreases the emotional processing of negative stimuli, in terms of decreased cardiac and electrodermal reactivity, fewer ratings of emotional significance, and decreased emotional memory performance.

In the present study, we used LF and HF rTMS to the right dlPFC in a homogeneous sample of healthy women, and investigated the after-effects of both stimulation frequencies on the emotional perception and memory of affective picture materials, and their influence on ANS using the investigation of cardiac and skin conductance response. Emotional regulation in the context of this study includes regulation of sensory perception, arousal and valence, evoked by an emotional stimulus such as the contemplation of pictures with emotional contents.

Methods

Participants

Forty healthy women (right handed, age (mean ± SD) 24 ± 2.8 years) were included. Participants were recruited from medical students from the University Medical Center in Rostock, Germany. The exclusion criteria were somatic or psychiatric disorders, any kind of medication, and drug abuse. To assess psychopathology, we used the Structured Clinical Interview for DSM-IV, SKID I (Wittchen et al. 1997). In addition, we used a number of self-report questionnaires, including the following scales: The Positive Affect and Negative Affect Schedule (PANAS) (Watson et al. 1988), the Empathizing, Systemizing and Autism-Spectrum Quotient (EQ, SQ, and AQ) (Baron-Cohen et al. 2003; Baron-Cohen and Wheelwright 2004; Baron-Cohen et al. 2001), the Beck Depression Inventory (BDI) (Beck et al. 1961), the NEO-Five Factor Inventory (NEOFFI) (Costa and McCrae 1992), and the trait scale of the State-Trait Anxiety Inventory (STAI-Trait, see Table 1) (Spielberger and Vagg 1984). All participants signed a written informed consent form and received an expense allowance. The study was carried out in accordance with the declaration of Helsinki and with the approval of the institutional review board of the University of Rostock.

Study design

In a single-blind, placebo-controlled, cross-over-design, participants underwent rTMS stimulation twice, with an interval of 2 weeks, once with a real and once with a placebo (sham)-TMS coil. The participants were randomly assigned to one of two groups of each 20 subjects. One group received a single application of 10 Hz rTMS, the other group received 1 Hz rTMS. Each real rTMS application was crossover-balanced with a placebo stimulation 14 days before or after the real rTMS application. Ten minutes after each rTMS session, emotionally salient pictures were presented to the participants, while they were asked to rate the arousal and the valence of the presented pictures. Additionally, heart rate and skin conductance were measured (for details see below). Immediately prior to the second application of the rTMS, the participants' self-paced recall of pictures shown after the first rTMS application was assessed (flow chart of study design in Fig. 1).

Table 1 Psychometric description of sample

	RTMS type				*p* value
	10 Hz ($n = 20$)		1 Hz ($n = 20$)		
	Mean	SD	Mean	SD	
Age	23.55	2.58	23.30	2.92	0.77

Scale	Value				
PANAS-State	Positive affect	36.42	2.93	35.90	2.95	0.58
	Negative affect	19.05	7.11	21.05	5.56	0.33
STAI-Trait	Sum	39.25	9.01	38.35	7.77	0.73
NEO-FFI	Neuroticism	19.95	8.54	19.80	6.76	0.95
	Extraversion	31.00	6.27	28.15	5.59	0.13
	Openness	32.20	4.32	29.20	6.48	0.09
	Tolerability	33.40	4.97	31.80	5.25	0.32
	Conscientiousness	31.80	9.66	30.45	6.36	0.60
BDI	Sum	8.45	8.60	4.60	4.43	0.08
ESAQ	Empathizing	38.90	10.20	37.85	8.48	0.72
	Systemizing	20.35	7.94	22.05	6.17	0.45
	Autism	14.50	6.40	13.40	3.55	0.79

p value represents the level of significance in a two sample *t* test, there was no significant difference between the rTMS groups in any of the scales

rTMS repetitive transcranial magnetic stimulation, *SD* standard deviation, *PANAS* Positive and Negative Affect Schedule, *STAI* State-Trait-Anxiety-Inventory, *NEO-FFI* Five-Factor-Personality Inventory, *BDI* Beck Depressions Inventar, *ESAQ* Empathizing, Systemizing and Autism-Spectrum Quotient

Repetitive TMS parameter

Repetitive TMS was applied with a biphasic butterfly coil (MCF-B65, Magpro 30, MagVenture GmbH, Hückelhoven, Germany). At first the hot spot was determined as the point over the motor cortex where the TMS induced maximal motor evoked potentials (MEP) on the relaxed abductor pollicus brevis, measured by electromyography of the resting activity of the left thumb (Borckardt et al.

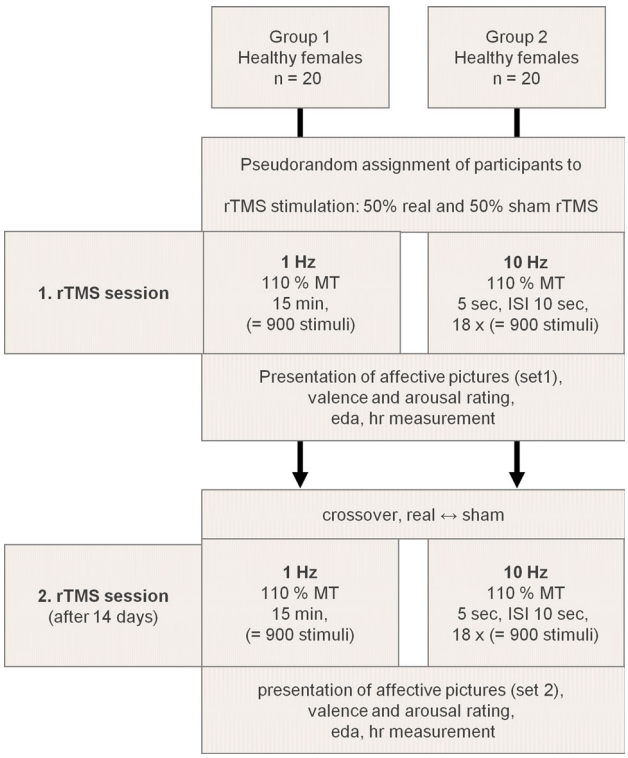

Fig. 1 Flow chart of study design. *MT* motor threshold, *sec* seconds, *min* minutes, *Hz* Hertz, *ISI* inter stimulus interval, *EDA* electrodermal activity, *HR* heart rate

2006). Second, the resting motor threshold (RMT) was defined as the TMS-intensity evoking MEPs of at least 50 μV in 5 out of 10 trials (Rossini et al. 1994). The standardised stimulation-point was placed over the right dlPFC, and was determined by positioning the TMS-coil 5 cm anteriorly to the point of RMT along a transverse plain to the obliquus superior (Herwig et al. 2001). The rTMS intensity was set to 110 % of the magnetic field strength evoking the individual RMT, both for the 1 Hz and for the 10 Hz group. The 10 Hz rTMS impulse train lasted 5 s, with an inter stimulus-interval of 10 s, and included 18 trains with 900 pulses in total, and had an overall duration of 4.5 min. The 1 Hz rTMS was applied continuously for 15 min with 900 pulses in total. During the sham rTMS condition, a shielded coil (MCF-P-B70, MagVenture GmbH Hückelhoven, Germany) was used. The coil's magnetic shield provides a field reduction of approximately 90 %. The sham TMS-coil was comparable to the verum TMS-coil in terms of shape and sound level.

Experimental paradigm

Ten minutes after finishing each rTMS application, the subjects were presented four categories of pictures from the "International Affective Picture System (IAPS)" (Lang et al. 2008): negative pictures with high and low arousal, positive pictures and neutral pictures. We aimed at comparing the effects along the arousal dimension within the negative stimulus category. Selection of pictures was based on normative ratings of IAPS stimulus set (Lang et al. 2008).

During the presentation, participants rated arousal/excitation and the pleasantness (valence) of each picture. A single trial had the following structure: presentation of the emotional picture (4 s), black screen (4 s), rating phase with variable duration, and finally a black screen (2 s). The pictures were rated on 9-point scales for emotional arousal and valence by selecting an icon of the "Self-Assessment Manikin Scale" via a keyboard (Bradley and Lang 1994). The sets of pictures (80 pictures per set in total and 20 items per emotional saliency category in each set) varied between the two rTMS sessions (verum versus sham rTMS). Picture presentation and response registration were controlled by Presentation 12.1 (Neurobehavioral Systems, Albany, CA, USA). Overall task duration depended on the duration of the self-paced rating phase, but all participants finished the task in less than 22 min.

Recognition task

Prior to the second rTMS-session, participants were presented with a surprise memory test. All pictures of the first rTMS-session and an equal number of new pictures were included. Every picture was shown, with the questions 'Have you already seen it?' answered with 'yes' or 'no' and 'How sure are you?'—assessed on a 5-level scale, by pressing a key. Regarding the second question, the 5-level scale was labelled from 1 to 5 as follows: 'very unsure', 'unsure', 'partly sure', 'sure', 'very sure'.

From the participants' answers, we inferred the recognition performance according to the signal detection theory (Green and Swets 1966) using the sensitivity index d', which basically represents the relative number of hits corrected by the relative number of false alarms. In addition, we assessed the mean confidence of the correct decisions, by calculating the mean response to the question 'How sure are you?' for each experimental condition.

Assessment of heart rate

The ECG signal was recorded according to Einthoven I with changes in accordance with Mason-Likar (Mason and Likar 1966) via the Variport TT System (1024 Hz sampling rate, Becker Meditec, Karlsruhe). The electrodes where placed under the left and right clavicle, and the grounding electrode was placed under the left anterior axillary line (ARBO Kiddy H 87 PG/F). R-peaks in the ECG signal were detected automatically, whereby the

accuracy of detection was controlled by visual inspection using BrainVision Analyzer 2.0 (BrainProducts, Gilching). The phasic changes in heart rate (phasic cardiac responses, PCR) in response to picture presentation were calculated from the ECG inter-beat intervals with the "Mean"-algorithm of the KARDIA software-package (Perakakis et al. 2010). The maximal decrease in PCR was determined for each picture category and used as a measurement of orientating or sensory perception during the 4 s of exposure to the pictures. (Sensory perception: sensory information that represents environmental objects is the basis for perceptional identification and interpretation processes. Sensory Perception is the first stage of these processes, aiming at recognition of (emotional) objects. Sensory perception can be distinguished from further appraisal of these objects, depending of the person's concept and expectations).

Assessment of skin conductance

Skin conductance was measured on the hypothenar eminence (dermatome 8) of the non-dominant hand with sintered 8 mm silver/silver chloride cup electrodes (E224A Mesmed GmbH, Munich), filled with non-hydrating isotonic electrolyte gel (0.05 M NaCl), in accordance with the recommendations for electro-dermal measurements (Boucsein et al. 2012; Fowles et al. 1981). The signal was recorded in DC-mode with the Varioport TT System (256 Hz sampling rate, Becker Meditec, Karlsruhe). The skin conductance data were analyzed with Ledalab 3.4.0 (Benedek and Kaernbach 2010). The mean amplitude of the phasic skin conductance response (SCR amplitude) during the 4 s of exposure to the pictures was calculated for each picture category.

Statistical analysis

All statistical analyses were carried out with SPSS 17 (IBM Corporation, NY, USA). In order To investigate the effect of rTMS on the physiological orientating response, assessment of valence and arousal, and recall ability dependent on emotional valence, 3-way-ANOVAs were calculated for each of the independent variables. RTMS-frequency (1 Hz versus 10 Hz) was run between subject factor and rTMS-type (sham versus verum) as well as stimulus category (high-arousal negative, low-arousal negative, positive, neutral), representing the two within-subject factors. We used the Greenhouse–Geisser correction in case the assumption of sphericity was rejected. When testing the heart rate responses to picture presentation for similarity between the picture categories, we compared the standard deviation of the mean heart rate responses to the four picture categories with t tests. In addition, we compared possible differences in the psychometric variables between the groups with two-sample t tests.

Results

Study sample

There was no significant difference between the groups (HF and LF rTMS group) in any of the demographic and psychometric scales. All participants can be characterized as non-depressed with normal range in BDI and were comparable in anxiety and personality traits (see Table 1).

Orienting responses of the autonomic nervous system (ANS)

Both the skin conductance response (SCR) and the phasic cardiac response (PCR) differed between the four stimulus categories (see Table 2), reflected by significant main effects for both PCR [$F(3,87) = 7.005$, $p < 0.001$] and SCR amplitude [$F(2.17,\ 73.83) = 4.77$, $p = 0.009$, see Table 3]. The decrease in PCR was the greatest for pictures with high arousal and negative valence and the least for pictures with positive valence (see Table 2; Fig. 2). The SCR amplitudes were the highest for both high-arousal negative as well as positive pictures and the lowest for neutral pictures (see Table 2; Fig. 3).

Repetitive TMS had an effect on PCR deceleration, as indicated by a significant 3-way interaction of rTMS-type, rTMS-frequency, and picture category [$F(3,87) = 3.305$, $p = 0.024$, see Table 3]. Post hoc t tests revealed that this interaction was driven by differences in responding to positive pictures in the 1 Hz verum rTMS condition with PCR deceleration to positive pictures significantly lower compared to all other picture categories [high-arousal negative vs. positive ($p = 0.002$), low-arousal negative vs. positive ($p = 0.025$) and neutral vs. positive ($p = 0.021$)]. In addition, in the 10 Hz verum rTMS was only significant for high negative–positive ($p = 0.03$) and interestingly after 1 Hz sham rTMS for positive–low negative ($p = 0.036$) and high negative–low negative ($p = 0.003$).

PCR deceleration averaged across 4 s of picture presentation differed less between the emotional categories after 10 Hz verum rTMS compared with 10 Hz sham rTMS ($p = 0.04$) and differed less at 2 ($p = 0.05$), 3 ($p = 0.01$) and 4 ($p = 0.02$) seconds of picture presentation after 10 Hz verum rTMS, compared with 1 Hz verum rTMS (see Fig. 2).

Table 2 Heart rate response and skin conductance response amplitudes to emotional picture presentation

RTMS stimulation	RTMS type	Picture valence	PCR in bpm		SCR AMP in µS	
			Mean	SD	Mean	SD
Placebo	HF	High negative	−2.39	2.02	0.069	0.103
		Low negative	−3.05	1.55	0.035	0.051
		Positive	−1.85	1.14	0.060	0.095
		Neutral	−2.54	1.7	0.031	0.058
	LF	High negative	−3.53	2.76	0.062	0.104
		Low negative	−2.81	2.88	0.035	0.061
		Positive	−2.59	2.66	0.053	0.082
		Neutral	−2.64	2.34	0.047	0.083
Verum	HF	High negative	−2.62	1.69	0.051	0.083
		Low negative	−2.53	1.62	0.039	0.091
		Positive	−2.18	0.88	0.053	0.085
		Neutral	−2.36	1.21	0.032	0.070
	LF	High negative	−3.71	2.33	0.064	0.110
		Low negative	−3.64	2.89	0.035	0.046
		Positive	−1.76	1.79	0.048	0.060
		Neutral	−3.14	2.21	0.036	0.047

PCR change of phasic cardial response in beats per minute; *SCR AMP* skin conductance response amplitude in µS, shown are the minimum of PCR and the maximum of SCR amplitude during 4 s of picture presentation; *SD* standard deviation

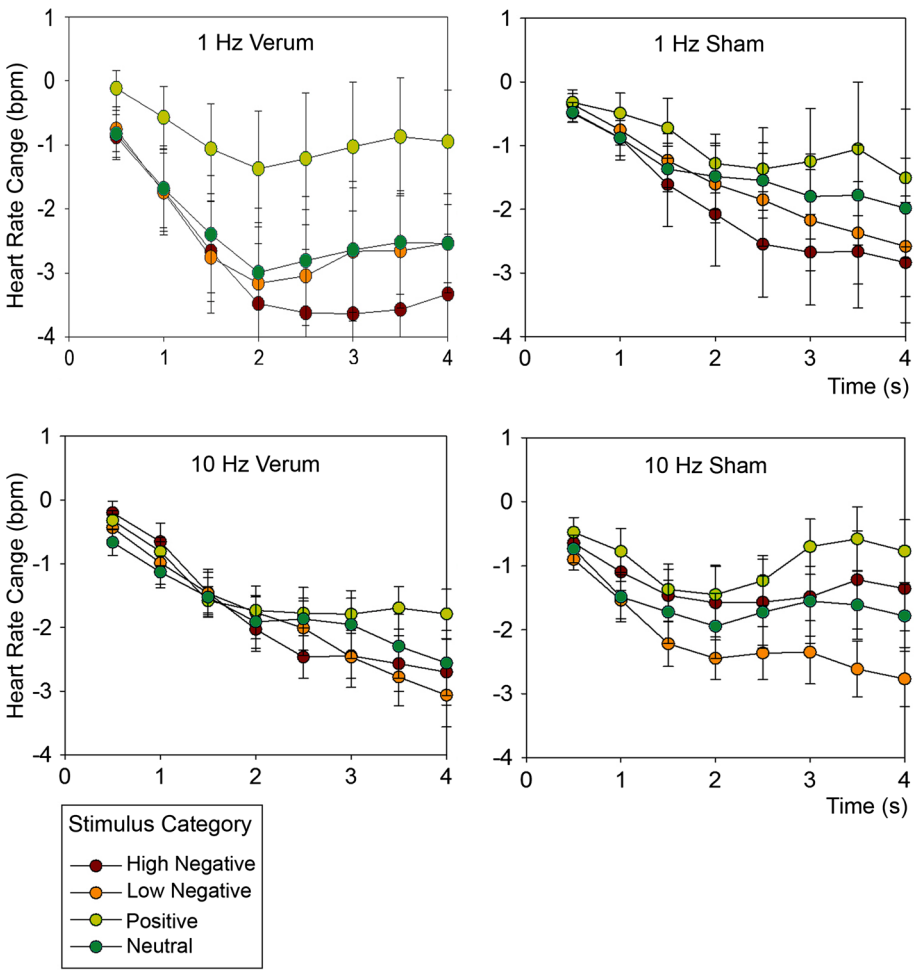

Fig. 2 Heart rate during picture presentation. Mean change in phasic cardiac response (PCR) for the first 4 s of picture presentation, as a function of picture category and rTMS condition. *bpm* beats per minute, *s* seconds. *Error bars* represent SEM

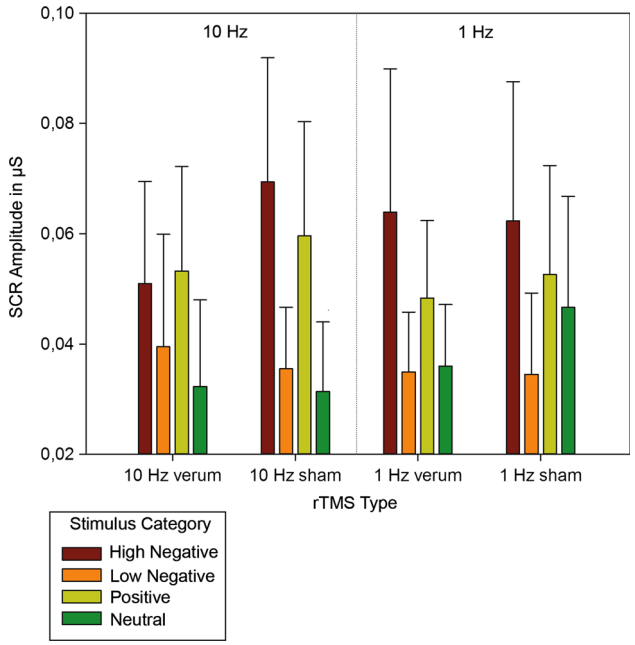

Fig. 3 Phasic skin conductance responses during picture presentation. Mean amplitude of phasic skin conductance response (SCR) in response to picture presentation, as a function of picture category and rTMS condition. *µS* microsiemens. *Error bars* represent SEM

Ratings of valence and arousal

The valence of the pictures was the most significant main effect with regard to the assessment of valence and arousal [valence-rating: $F(3, 55.62) = 462$, $p < 0.0001$ and arousal-rating: $F(3, 60.84) = 190$, $p < 0.0001$]. We found no difference in the assessment of picture rating between the rTMS-applications (see Tables 4, 5; Fig. 4).

Recognition of emotional pictures

We found no effect of rTMS on either the sensitivity d' or the level of confidence with which the reply was given. Sensitivity as well as subjective confidence of picture recognition was different for the emotional categories. There was a main effect of the picture category on the sensitivity [$F(3, 108) = 15.58$, $p < 0.0001$] and the level of subjective confidence [$F(3, 108) = 10.33$, $p < 0.001$]. The neutral valence pictures were recognized the least often, and the participants were also the least confident about their decision (see Tables 6, 7; Fig. 5).

Discussion

This randomized, placebo-controlled, cross-over study compared the effects of a single application of either 10 Hz rTMS with sham rTMS or 1 Hz rTMS with sham rTMS over the right dlPFC on emotional processing and autonomic responses in healthy women. To assess physiological reactivity to emotional stimuli, a bottom-up paradigm was used: participants were shown emotional pictures without a particular task (passive viewing). During the presentation of salient visual stimuli, independent of rTMS type, the ANS reacted with an increase in skin conductance and a phasic deceleration in heart rate, both reflecting a stimulus-directed attention. The sympathetically mediated increase in skin conductance represents primarily the initial attention capture (orienting response), whereas the parasympathetically mediated decrease in heart rate reflects continuing sensory processing (Bradley 2009). Our study showed a significant rTMS-effect on the orienting responses of the heart rate. This cardiac orienting response was significantly increased during the presentation of pictures with high- and low-arousing negative and neutral valence after 1 Hz rTMS compared to pictures with positive valence. In contrast, the modulatory effect of picture valence on cardiac orienting response was absent after 10 Hz rTMS. The orienting response in heart rate was not different between the emotional conditions, and the response was lower in general after 10 Hz rTMS.

This three-way interaction between picture category, rTMS stimulation and rTMS type appeared to be mainly driven by the fact that PCR (heart rate deceleration) after 1 Hz rTMS was more pronounced in response to high- and low arousal negative and neutral pictures compare to the positive pictures. The arousal of positive was similar to the arousal of neutral pictures, and both categories were less arousing than the two negative picture categories (see Table 4). Because valence of positive pictures differed from all other emotional categories, we infer that PCR differences between positive and the neutral/negative pictures might be mainly valence driven. However, nevertheless, because we did not include both high and low arousing positive stimuli, we cannot preclude that this interaction's effect on PCR was influenced by differences in arousal. In addition, independent of the frequency (1 versus 10 Hz), and the type of rTMS application (placebo versus active), a main effect of emotional picture category was evident in PCR (heart rate deceleration), SCR, in valence and arousal ratings and in picture memory (recognition task). The presentation of highly arousing negative pictures was accompanied by the most pronounced PCR deceleration and the highest SCR, whereas positive pictures elicited the lowest PCR and SCR reactions. Again, because we did not add a high arousal positive picture condition, we cannot unequivocally disentangle the effects of valence and arousal in the present data. A decrease in heart rate as an orienting response (OR) to unknown aversive stimuli has been described previously (Hare et al. 1970), however, with repeated picture

Table 3 Results of 3 way ANOVA with ANS measures as dependent variables

Effect	Dependent variable	*df*	*F*	*p*
Emotional category	PCR	(3, 87)	7.005	**0.0003****
	SCR amplitude	(2.17, 73.83)	4.77	**0.009***
Emotional category × rTMS type	PCR	(3, 87)	1.47	0.22
	SCR amplitude	(2.17, 73.83)	0.58	0.57
rTMS stimulation	PCR	(1, 29)	0.06	0.79
	SCR amplitude	(1, 34)	0.12	0.72
Emotional category × rTMS stimulation	PCR	(3, 87)	0.52	0.66
	SCR amplitude	(2.22, 75.52)	0.09	0.92
RTMS type × rTMS stimulation	PCR	(1, 29)	0.15	0.7
	SCR amplitude	(1, 34)	0.38	0.53
Emotional category × RTMS type × rTMS stimulation	PCR	(3, 87)	3.30	**0.02***
	SCR amplitude	(2.22, 75.52)	0.19	0.84

df degree of freedom; *PCR* phasic cardial response; *SCR* amplitude skin conductance response amplitude; *rTMS* repetitive transcranial magnetic stimulation, stimulation = placebo or verum, type = 1 or 10 Hz

** $p < 0.001$

* $p < 0.05$

presentation habituation occurs (Bradley 2009). Our results are in accordance with a previous study reporting heart rate responses but not skin conductance being affected by rTMS (van Honk et al. 2003), possibly indicating a specific effect of rTMS on the parasympathetic nervous system during emotion perception. Furthermore, using frontal transcranial direct current stimulation (tDCS), Brunoni and colleagues (2013) reported effects of simultaneous bifrontal modulation using tDCS on heart rate variability (HRV) during processing of negative emotional pictures (Brunoni et al. 2013). During left anodal tDCS and while viewing emotional negative stimuli, which facilitated left frontal cortical activity and attenuated right frontal activity, higher activation of the parasympathetic nervous system could be observed. Although tDCS is a different technique and Brunoni and colleagues stimulated the bifrontal cortex,

Table 4 Mean values and standard deviations of valence and arousal ratings

RTMS type	RTMS stimulation	Picture valence	Valence		Arousal	
			Mean	SD	Mean	SD
Placebo	HF	High negative	7.38	0.55	6.51	1.19
		Low negative	6.77	0.64	5.46	1.05
		Positive	2.65	0.75	2.82	0.89
		Neutral	4.38	0.49	2.39	1.04
	LF	High negative	7.2	0.51	6.15	1.11
		Low negative	6.57	0.5	5.21	1.16
		Positive	3.1	0.76	3.44	1.09
		Neutral	4.4	0.58	2.71	1.21
Verum	HF	High negative	7.39	0.65	6.36	1.72
		Low negative	6.77	0.68	5.47	1.52
		Positive	2.56	0.79	2.87	1.06
		Neutral	4.35	0.42	2.35	1.00
	LF	High negative	7.25	0.62	6.45	1.12
		Low negative	6.69	0.54	5.52	1.23
		Positive	3.09	0.69	3.34	0.96
		Neutral	4.44	0.43	2.74	1.2

rTMS pulse interval, valence and arousal ratings were given on a 9-level Self Assessment Manikin (SAM) Scale (Bradley and Lang 1994)

SD standard deviation, *HF* high frequency (10 Hz), *LF* low frequency (1 Hz)

Table 5 Results of 3-way ANOVA with valence and arousal picture ratings as dependent variables

Effect	Dependent variable	*df*	*F*	*P*
Emotional category	Valence	(1.46, 55.62)	462.05	**<0.0001****
	Arousal	(1.6, 60.84)	190.57	**<0.0001****
Emotional category × rTMS type	Valence	(1.46, 55.62)	2.70	0.09
	Arousal	(1.6, 60.84)	1.49	0.23
rTMS stimulation	Valence	(1, 38)	0.01	0.91
	Arousal	(1, 38)	0.26	0.61
Emotional category × rTMS stimulation	Valence	(1.96, 74.66)	0.26	0.77
	Arousal	(1.92, 73.19)	0.83	0.43
RTMS type × rTMS stimulation	Valence	(1, 38)	1.42	0.24
	Arousal	(1, 38)	0.70	0.41
Emotional category × rTMS type × rTMS stimulation	Valence	(1.96, 74.66)	0.13	0.87
	Arousal	(1.93, 73.19)	1.28	0.28

df degree of freedom; *rTMS* repetitive transcranial magnetic stimulation, stimulation = placebo or verum, type = 1 or 10 Hz

** $p < 0.001$

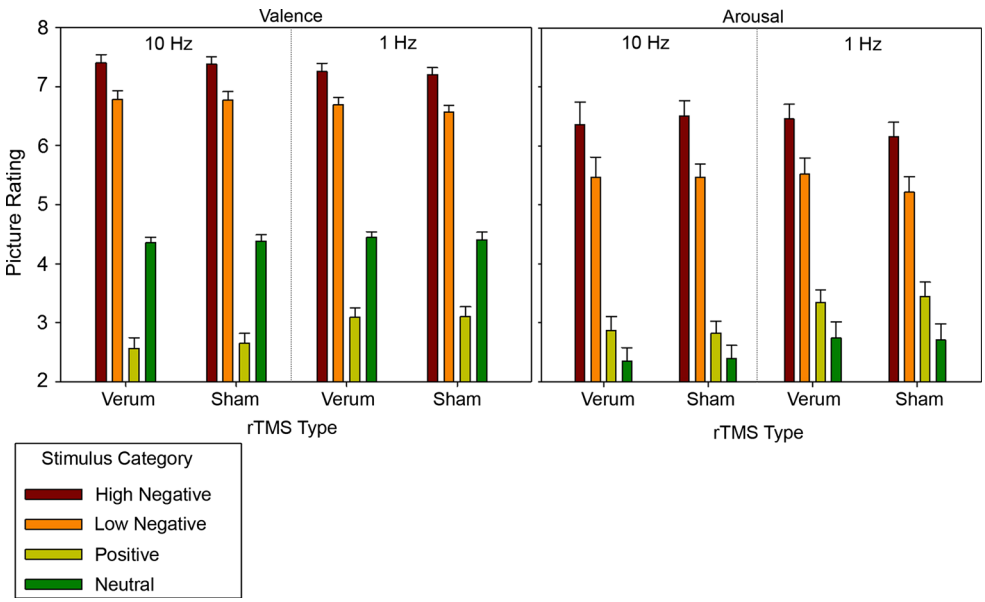

Fig. 4 Assessment of valence and arousal. Mean ratings of valence and arousal, as a function of picture category and rTMS condition, measured on 9-level scales, 9 = positive valence and strong arousal; *error bars* represent SEM

their findings are consistent with the present findings: inhibiting right dlPFC activity increases parasympathetic activity while viewing negative emotional stimuli.

It should be noted, that we found differences in PCR after 1 Hz sham rTMS for positive–low negative pictures and high negative–low negative pictures, while there were no differences between the stimulus categories after 10 Hz sham rTMS. Nevertheless, these effects seem to be marginal because both sham conditions were not different in a direct statistical comparison. However, minor differences between both sham conditions (1 and 10 Hz) regarding sensory phenomena cannot be excluded.

In regard to the presumed underlying neural pathways, our results might be interpreted as follows: The inhibitory effect of 1 Hz rTMS (Chen et al. 1997) over the right dlPFC indirectly results in disinhibition of the amygdala, which leads to enhanced sensory perception and the assessment of stimuli without pleasant saliency, including aversive and neutral valence compared to the positive valence. This, in turn, is reflected in a higher decrease in heart rate during the presentation of pictures with negative and neutral emotional valence compared to neutral pictures. In contrast, application of 10 Hz rTMS "level" this effect of emotional saliency in sensory perception, as differences in heart rate orienting response were less different between the emotional categories after HF rTMS. This would be in line with the proposed facilitating effect of HF rTMS on the dlPFC (Maeda et al. 2000), as well as an

Table 6 Mean values and standard deviations of sensitivity d' and level of confidence

Picture valence	RTMS stimulation	RTMS type	Sensitivity d'		Level of confidence	
			Mean	SD	Mean	SD
High negative	Placebo	HF	2.43	0.21	3.77	0.03
		LF	2.11	0.40	3.94	0.01
	Verum	HF	2.86	0.17	3.66	0.01
		LF	2.47	0.11	3.76	0.01
Low negative	Placebo	HF	2.65	0.18	3.61	0.03
		LF	2.85	0.26	3.92	0.04
	Verum	HF	3.43	0.33	3.64	0.03
		LF	3.02	0.13	3.51	0.02
Positive	Placebo	HF	2.06	0.09	3.72	0.03
		LF	2.26	0.20	4.00	0.01
	Verum	HF	2.64	0.14	3.80	0.03
		LF	1.88	0.06	3.72	0.01
Neutral	Placebo	HF	1.36	0.16	3.45	0.05
		LF	1.39	0.07	3.70	0.01
	Verum	HF	1.37	0.12	3.40	0.04
		LF	1.30	0.03	3.47	0.02

d' (sensitivity according to signal detection theory) = z(hits relative) − z(false alarms relative)

SD standard deviation

Table 7 Results of 3-way ANOVA with sensitivity d' and level of confidence as dependent variables

Effect	Dependent variable	*df*	*F*	*p*
Emotional valence	d'	(3, 108)	15.57	**<0.0001****
	Confidence	(3, 108)	10.33	**<0.0001****
Emotional valence × rTMS type	d'	(3, 108)	0.49	0.68
	Confidence	(3, 108)	0.15	0.92
rTMS stimulation	d'	(1, 36)	0.48	0.49
	Confidence	(1, 36)	0.57	0.45
Emotional valence × rTMS stimulation	d'	(3, 108)	0.20	0.89
	Confidence	(3, 108)	1.35	0.93
RTMS type × rTMS stimulation	d'	(1, 36)	0.60	0.44
	Confidence	(1, 36)	0.62	0.43
Emotional valence × RTMS type × rTMS stimulation	d'	(3, 108)	0.39	0.76
	Confidence	(3, 108)	0.95	0.41

d' (sensitivity according to signal detection theory) = z(hits relative) − z(false alarms relative)

df degree of freedom; *rTMS* repetitive transcranial magnetic stimulation, stimulation = placebo or verum, frequency = 1 or 10 Hz

** $p < 0.001$

enhancement of cognitive control processes in the frontal-limbic emotional circuit. Indeed, corresponding to this finding, improved cognitive control has been previously observed in anxiety disorders after HF rTMS over the dlPFC (Paes et al. 2013; Rossi et al. 2006). It should be noted that our results seem to be at odds with the results of three studies of a Belgian research group (De Raedt et al. 2010; Leyman et al. 2009; Vanderhasselt et al. 2011), who showed enhanced attentional bias to angry faces after HF rTMS over the right dlPFC. Additionally, De Raedt et al. (2010) showed that disengagement from angry faces was associated with decreased activation within the right dlPFC and the dorsal anterior cingulum (dACC) and increased activity in the right amygdala. In contrast to these studies, which investigated guided attention control in reaction-time-paradigms, our study required passive viewing of emotional pictures. Sensory perception is directly mediated by frontal brain regions via cortico–pulvino–cortical

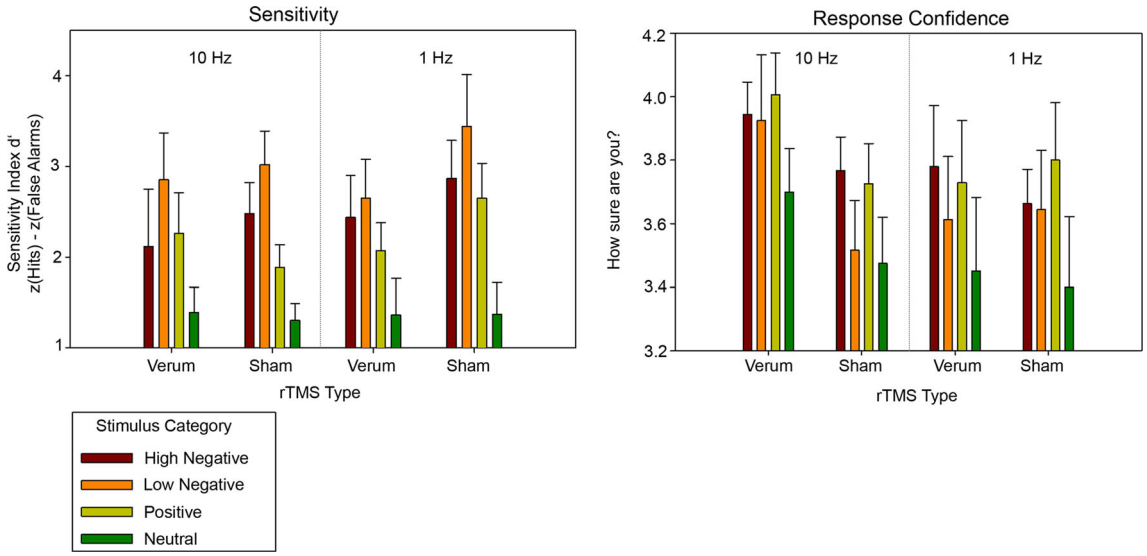

Fig. 5 Recall of pictures after 14 days of intervention. Mean sensitivity d' according to the signal detection theory (in z values) and the confidence of answers (scale 1 = very unsure, to 5 = very sure), as a function of picture category and rTMS condition; *error bars* represent SEM

connections (Pessoa and Adolphs 2010) and direct links between the mediodorsal thalamus and frontal regions, including the dlPFC (Klein et al. 2010). Therefore, the effect of rTMS over the right dlPFC on emotion processing might be modulated by different activity states of the dlPFC in guided and unguided attention control. Additionally, the effects of LF-rTMS over the dlPFC on guided attention control were not tested in our study, thereby rendering a direct comparison impossible. Apart from the effect of rTMS on the sensory perception of emotional pictures, we could not identify other rTMS effects on further emotional processing: neither the assessment of valence and arousal immediately following the picture presentation nor the recognition of pictures after 2 weeks were affected by rTMS application. Therefore, the modulation of the orienting response (PCR deceleration) in the present study concurs with previous studies, which have reported modulation of attention to aversive pictures following rTMS over the right dlPFC (Baeken et al. 2006). However, these attentional effects did not result in changes with regard to the conscious evaluation of the presented emotional stimuli in the present study. Our study might encourage future research on the possible effects on different rTMS paradigms on emotion processing and on ANS functioning. We conducted a well-balanced cross-over study design regarding rTMS with placebo and verum condition in a very homogenous group of young healthy women.

However, a major limitation was the small sample size regarding analysis of covariates, such as the possible influences of different intrinsic neuronal activity profiles of the stimulated cortex, as studies have shown effects of the cortical excitation level before (Bagnato et al. 2005) and during (Ziemann et al. 1998) rTMS stimulation on the post-rTMS effects in the motor cortex. A further limitation is the lack of a pre-rTMS emotion recognition experiment. However, habituation effects in response to attenuated stimulus saliency when performing pre- and post-rTMS should be avoided. Nevertheless, further research could investigate pre- and post-rTMS effects on emotional processing, including additional stimulus sets and a shorter experiment duration with a decreased number of emotional categories to avoid a decrease in stimulus saliency.

Conclusions for clinical practice

In sum, our study of very homogenous groups of young healthy women shows that a single application of rTMS over the right dlPFC has an effect on phasic heart rate responses, a marker of the ANS for sensory orientiation during the processing of emotional visual stimuli. However, rTMS had no effect on further emotional processing, neither on subjective appraisal in terms of valence and arousal nor on later recognition of pictures. From our results it can therefore be concluded that rTMS modulates the cortical excitability of the right dlPFC in a frequency dependent manner, resulting in opposite effects on the ANS activity during emotional processing, likely via top-down regulation of the amygdala activity involving fronto-limbic connections. The influence on the orienting response may result from modified interaction of the dlPFC with the amygdala, a circuitry that serves as the neural basis for emotion processing and emotion regulation. Along with potential effects of rTMS on general improvement of

perception (Levasseur-Moreau et al. 2013), our study encourages the investigation of rTMS effects on emotional processing in the different contexts of voluntary and involuntary attention. These studies might help us to understand the mechanisms underlying the reported effects of rTMS on affective symptoms in depressive patients previously reported (Berlim et al. 2013, 2014; Hoeppner et al. 2010; Hovington et al. 2013).

Compliance with ethical standards

Conflict of interest No conflicts of interest are declared.

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