

# Chronometric features of processing unpleasant stimuli: a functional MRI-based transcranial magnetic stimulation study

Tina Kaffenberger<sup>a,d</sup>, Thomas Baumgartner<sup>b,c</sup>, Susan Koeneke<sup>b</sup>, Lutz Jäncke<sup>b</sup> and Uwe Herwig<sup>a,d</sup>

<sup>a</sup>Psychiatric University Hospital, <sup>b</sup>Department of Psychology, Institute for Neuropsychology, <sup>c</sup>Institute for Empirical Research in Economics, University of Zurich, Zurich, Switzerland and <sup>d</sup>Department of Psychiatry, University of Ulm, Ulm, Germany

Correspondence to Professor Dr Uwe Herwig, MD, Psychiatric University Hospital, Lenggstr. 31, CH-8032 Zürich, Switzerland  
Tel: +41 44 384 3375; fax: +41 44 383 4456; e-mail: uwe.herwig@puk.zh.ch

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The quick identification of potentially threatening events is a crucial cognitive capacity to survive in a changing environment. Previous functional MRI data revealed the right dorsolateral prefrontal cortex and the region of the left intraparietal sulcus (IPS) to be involved in the perception of emotionally negative stimuli. For assessing chronometric aspects of emotion processing, we applied transcranial magnetic stimulation above these areas at different times after negative and neutral picture presentation.

An interference with emotion processing was found with transcranial magnetic stimulation above the dorsolateral prefrontal cortex 200–300 ms and above the left intraparietal sulcus 240/260 ms after negative stimuli. The data suggest a parallel and conjoint involvement of prefrontal and parietal areas for the identification of emotionally negative stimuli. *NeuroReport* 19:777–781 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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## Introduction

In everyday life, we are easily able to identify an emotionally negative meaning of a sudden event and to initiate adequate reactions. This capacity helps to survive in possibly dangerous and suddenly changing environments. In the case of a sudden visual event or scene with a negative impact, for example, a threatening person, the information has to be processed on several central nervous stages including cortical areas within milliseconds to react adequately. The brain areas involved in the identification of negative stimuli have been assessed in several studies based, for instance, on functional neuroimaging [1]. However, little is known about the chronometry of information flow during emotion processing. Chronometric features of cortical information processing can be investigated by combining the advantages of the good spatial resolution of functional MRI (fMRI) and of the high temporal resolution of transcranial magnetic stimulation (TMS). As a noninvasive virtual lesion method, TMS allows to interfere with the cortical information processing by inducing neuronal depolarization in a cortical region of interest. It enables to test the temporal dynamics of these regions and to address their involvement in a task-specific demand [2].

According to data from an earlier fMRI study [3], the right dorsolateral prefrontal cortex (DLPFC) and the region around the left intraparietal sulcus (IPS) are activated during the perception of emotionally negative visual stimuli. Both regions are known to respond to the emotional significance of a stimulus [1,4,5] and are assumed to be part of emotion processing pathways. We hypothesized an

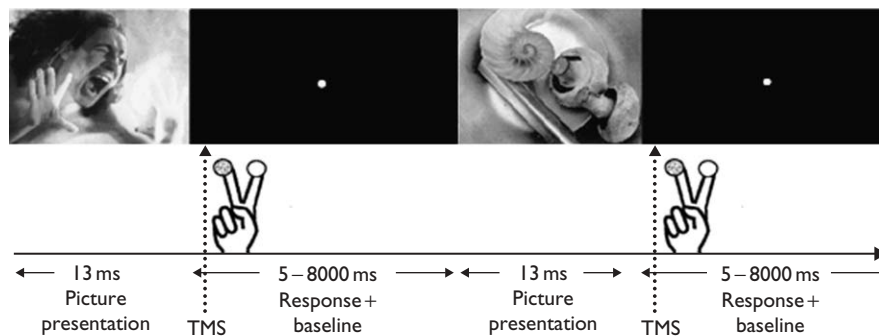
interfering influence of TMS when applied above these regions at critical time points during the processing of emotionally negative visual stimuli as reflected by altered behavioural parameters.

## Methods

Fourteen healthy volunteers (eight women, age 19–36 years, 13 right-handed) participated in the TMS experiment. Exclusion criteria were neurological or psychiatric diseases, pregnancy, substance abuse, current medication, a history of epileptic seizures, brain trauma or brain surgery. Written informed consent was obtained from all volunteers after full description of the study that was approved by the local ethics committee.

## Experimental design

Volunteers performed a stimulus–reaction task during which pictures with randomly unpleasant or neutral emotional content had to be identified quickly (Fig. 1). They were instructed to press one of two response buttons according to the emotional content of the pictures as fast as possible. The allocation of the response buttons to the emotional meaning was varied randomly among the volunteers. The duration of picture presentation was 13 ms, conforming to the minimum time period necessary for identifying the emotional content. Between the trials, a fixation point was presented for 5000 ms. TMS was applied at six different times after picture presentation [stimulus onset asynchronies (SOAs)]. For each of the six



**Fig. 1** In a stimulus–reaction task, negative or neutral pictures were presented randomly for a period of 13 ms. Volunteers had to evaluate the pictures according to their emotional content by pressing one of two response buttons. TMS, transcranial magnetic stimulation.

SOAs, volunteers were presented sets of six pictures of either negative or neutral valence for both stimulation sites (DLPFC, IPS), resulting in a total of 144 trials. The pictures (International Affective Picture System [6]) were arranged to match complexity, valence and arousal for the emotion conditions. Importantly, they were also matched within the sets according to the reaction times (RTs) necessary for the identification as revealed in a pretest with 18 healthy volunteers (data not shown), to allow for similar mean RTs of the sets. The attribution of these sets to the different SOAs was individually randomized for each volunteer.

#### Stimulation sites

Stimulation sites were revealed by an earlier fMRI study investigating the activated brain regions in a task during which volunteers expected and then perceived emotional pictures of negative, neutral and positive content (for detailed methods see Ref. [3]). For this study, we considered a group analysis of the contrast ‘presentation of unpleasant pictures versus presentation of neutral pictures’ ( $P < 0.00001$ , corrected; not reported in the previous study). This analysis revealed the right DLPFC (Talairach coordinates 39/26/47, Brodmann area BA 9) and the left IPS region (–38/–62/47, BA 7) to be activated more strongly during the perception of negative emotional stimuli compared with the neutral stimuli.

#### Transcranial magnetic stimulation

TMS was applied using a TWIN TOP magnetic stimulator (Medtronic, Düsseldorf, Germany) with an 8-shaped focal coil (MC-B70). We applied double-pulse TMS with an interstimulus interval of 20 ms to obtain a more prominent interference in regards to the one achievable with single pulses. Both subsequent pulses were applied with the same intensity of 120% of the resting motor threshold [7] (in four volunteers with 110% owing to the individual tolerance). The positioning of the TMS coil on the volunteers’ heads was determined using the international 10–20 system for EEG electrode placement. The coordinates of the fMRI activation centres within the right DLPFC and the left IPS region were projected onto the scalp surface by transformation into the congruent electrode positions of the 10–20 system [8]. This resulted in a good approximate value within the range of 1 cm in a TMS application over F4 (right DLPFC) and P3 (left IPS). The coil was held tangentially on the scalp with the centre above F4 and P3 and the handle pointing 45° posterior to the mid-sagittal line. The coil was placed stabilized to the volunteer’s immobilized head. The

comparison between the stimulations at different SOAs and between the emotion conditions negative and neutral served as internal control. Thus, we avoided misinterpretations of the data owing to different outcomes of the dependent variables resulting from different discomfort of TMS when using control conditions at other cortex areas or sham stimulation [9]. Double-pulse TMS was randomly delivered at six parametrically varied SOAs after picture presentation. Given the possibility of information processing involving firstly the IPS region and later on the DLPFC, we set the first SOA for the IPS earlier than for the DLPFC, with a main period of common SOAs (IPS 40/60, 80/100, 120/140, 160/180, 200/220 and 240/260 ms; DLPFC 80/100, 120/140, 160/180, 200/220, 240/260 and 280/300 ms). The baseline period of 5000 ms between trials was implemented to avoid carry-over effects of TMS.

#### Analysis

Error rates (ERs) and RTs were obtained for each volunteer at each SOA for negative and neutral pictures as dependent variables. Responses were scored as errors in the case of a wrong response or no response during a time period of 300–3000 ms after picture presentation. We calculated average values for ERs and RTs for each SOA of both emotional valences at the two stimulation sites over all volunteers. As a result of the non-normal distribution of the behavioural data as assessed with Kolmogorov–Smirnov tests, we performed analyses with nonparametric statistical tests. First, we performed a Friedmann test to compare the overall RTs and ERs between the different stimulation times of one emotional stimulus separately for both stimulation sites. In the second step, we performed two-tailed Wilcoxon tests comparing the average values of the RTs and the ERs for each SOA with the average values of all other SOAs of the same emotional condition and the same stimulation site. Further, we compared these average values achieved for the negative condition with the same SOA-related averages obtained for the neutral condition. All analyses were performed separately for both stimulation sites and the significance level was set at  $P < 0.05$  for all comparisons.

#### Results

Fourteen healthy volunteers participated in the TMS experiment. Twelve volunteers were included in the analysis (six women, age 19–36 years). One volunteer was excluded owing to technical problems during task performance, one was excluded because she showed ERs of about

50%, equalling a random response pattern, and reported the nonidentification of most pictures.

For the DLPFC, the Friedmann test showed significant differences between RTs derived from trials with different SOAs for stimulation after the presentation of negative pictures ( $\chi^2=12.67$ ,  $df=5$ ;  $P=0.02$ ). In contrast, it did not point out comparable results for neutral pictures ( $\chi^2=0.86$ ,  $df=5$ ;  $P=0.98$ ). According to the Wilcoxon test, stimulation applied over the DLPFC 240/260 ms after presentation of negative pictures resulted in increased RTs when compared with stimulation at 80/100 ms ( $P=0.03$ ), 120/140 ms ( $P=0.01$ ) and 160/180 ms ( $P=0.03$ ). Furthermore, stimulation above the DLPFC 200/220 ms ( $P=0.02$ ) and 280/300 ms ( $P=0.03$ ) after presentation of negative pictures also resulted in increased RTs when compared with stimulation at 80/100 ms. The comparison of RTs of the neutral condition did not reveal any differences (Fig. 2a).

For the IPS region, the Friedmann test pointed out a trend towards a RT difference between different SOAs after the presentation of negative pictures ( $\chi^2=9.67$ ,  $df=5$ ;  $P=0.08$ ), whereas a comparable trend cannot be reported for neutral pictures ( $\chi^2=7.38$ ,  $df=5$ ;  $P=0.2$ ). Stimulation applied above the IPS 240/260 ms after negative picture presentation resulted in increased RTs compared with the other SOAs: versus 40/60 ms,  $P < 0.05$ ; versus 80/100 ms,  $P=0.02$ ; versus 120/140 ms,  $P=0.07$ ; versus 160/180 ms,  $P=0.02$ ; versus 200/220 ms,  $P=0.02$  (Fig. 2b). Further, the stimulation at this SOA of 240/260 ms also showed increased RTs in comparison to the same SOA after presentation of neutral pictures ( $P=0.04$ ).

The analysis of the ERs showed no significant differences in any condition.

## Discussion

The purpose of our study was to investigate chronometric aspects of the processing of negative emotional stimuli. Our data indicate a TMS-induced interference with the identification process of negative emotional pictures in the right DLPFC in a time period from 200 to 300 ms with a peak at 240/260 ms after picture presentation compared with earlier SOAs, as indicated by differing RTs. In addition, we found evidence for a TMS-induced influence on the left IPS region, focusing on 240/260 ms after negative picture presentation in comparison with the other SOAs as well as compared with the same SOA of the neutral condition. In contrast, we did not find any TMS-induced interference regarding the recognition of neutral pictures. These findings also verify the accordant previous fMRI results. Considering the temporally parallel interference, our results point to a parallel conjoint involvement of both areas within the identification process of the negative valence of visual emotional stimuli.

Several studies have used TMS to investigate the cortical processing of emotions [10–12]. The chronometry of emotion processing, to our best knowledge, has not yet been addressed and only one study investigated chronometric aspects of working memory processing [13].

The right DLPFC was hypothesized to adopt among other functions such as response planning and executive control [14] a role in mood control, and was shown to be associated with the processing of negative emotions such as sadness and fear in healthy and depressed persons [15]. Further, the DLPFC was described to be involved in an affective

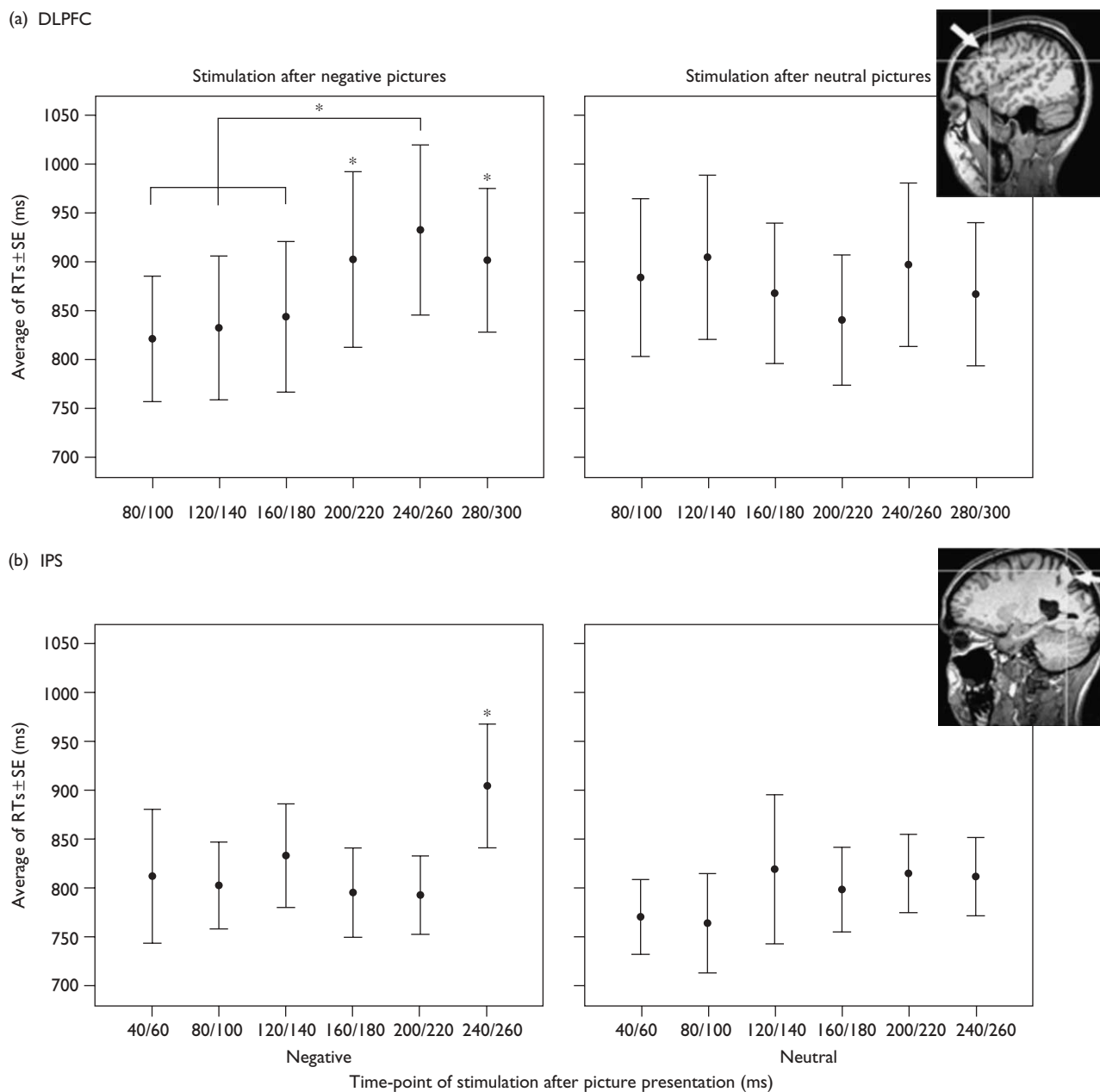
response generation circuit [16] and in emotion regulation processes [17]. Likewise, the left IPS region was suggested to be associated with the processing of negative emotions as it was involved in attention processes toward fearful emotional stimuli or an emotional stroop task [18,19]. Our findings may thus result from TMS interference with the processing of the emotional content of the stimuli as well as with the attentional function of the IPS region in identifying potentially threatening events.

Regarding processing pathways for negative emotional stimuli, our findings may be interpreted in the frame of recognition models for the emotional meaning of exterior objects based on the coexistence of a sequential activation of cortical regions and a subcortical projection. Thereby, the emotional stimulus may proceed sequentially after visual perception via retina, lateral geniculate body and primary and associative visual areas further to parietal regions as the IPS for increasingly higher-level stimulus analysis. Thus, the left IPS region could be shown to be critically involved at 240/260 ms after stimulus in the course of negative emotion processing. Of course, it may be activated also earlier with higher redundancy or for processing other features. Assuming further upstream propagation of the IPS information, efferent pathways of the IPS region may target the DLPFC [20], which may be responsible for the TMS interference in the DLPFC until 280/300 ms after picture presentation. The observed delay in the emotional information processing caused by TMS above the DLPFC earlier as, and simultaneously to the IPS region activation, would fit with assumptions of an additional subcortical projection for the emotional input finally targeting the DLPFC supposedly via amygdala and other prefrontal areas [21]. Within this pathway, the emotional meaning may prime a first preconscious alertness toward the stimulus on the subcortical level and it may induce physiological conditions serving to react as quickly as possible as soon as further details are being processed [21]. The DLPFC may keep the information active for later decision making. Further incoming information of more detailed processing from the IPS region may serve for verification and specification of the initial information. The DLPFC may further provide top-down biasing information to the IPS region for verification purposes and conjoint information processing [22], and also to motor areas for urgent motor action before a detailed processing. Finally, after integration and adjustment of all incoming information, the DLPFC may pose as a central executive and decision maker to transfer the appropriate command to the premotor and motor cortex for initiation of the demanded reaction [14,23].

## Limitations

A stereotaxic approach on the single volunteer level might have resulted in an even more precise localization. However, the 10-20 method would not have exceeded a possible inaccuracy within a centimetre range [8]. Taking further note of the spatial field of TMS interferences of several square centimetres [24] as well as the emotion-specificity of our results, we assumed that the relevant activation spot was targeted.

For the IPS region, we found an increase in RTs for the latest stimulation time (240/260 ms). The chosen stimulation intervals for IPS and DLPFC did not cover times later than 300 ms as we attempted to avoid an interference of TMS



**Fig. 2** Descriptive presentation of the reaction times (RTs) with standard errors (SE) owing to stimulation at different stimulus onset asynchronies (SOAs) after negative (on the left) and neutral picture presentation (on the right). \*Significance  $P < 0.05$ . (a) Stimulation of the right dorsolateral prefrontal cortex (DLPFC, functional MRI cluster marked with arrow) 240/260 ms after presentation of negative pictures resulted in increased RTs when compared with stimulation at 80/100, 120/140 and 160/180 ms. Stimulation at 200/220 and 280/300 ms resulted in increased RTs when compared with stimulation at 80/100 ms. No differences within the neutral condition. (b) Intraparietal sulcus (IPS, fMRI-cluster marked with arrow): Stimulation 240/260 ms after negative picture presentation resulted in increased RTs compared with all other SOAs as well as in comparison to the same SOA of the neutral condition.

with the motor responses of which the earliest occurred after about 300 ms. Hence, later emotion-specific activations of the IPS could not be specified.

We did observe TMS-induced influence on RTs, but not on ERs. Although it was suggested that RTs might be more susceptible to TMS effects on cognitive tasks than ER measurements [25], others demonstrated interferences with working memory on ERs, but not on RTs [13]. We found increased RTs for negative pictures only, underlining an

emotion-specific effect. It may be argued that a redundant information processing may cause the lacking influence on ERs and that the increased RTs result from a time-consuming process of compensating noise in the local activity induced by the depolarization owing to TMS. Accordingly, a TMS interference may interrupt the propagation of emotional information and thus delay final decision-making and RT. However, it won't erase the information, thus not leading to increased ERs.

## Conclusion

We found an emotion-specific effect of TMS at distinct stimulation times during the processing of pictures with a negative affective valence. The DLPFC was susceptible to TMS parallel to and earlier than the IPS region, which would fit with concepts of a parallel emotion processing including subcortical and transcortical propagation of information flow. Notably, the involvement of the right DLPFC and the left IPS region in negative emotion processing was demonstrated and thus cross-verified with two different methods, fMRI and TMS. The applied methodological approach to study chronometric features of emotion processing may also serve for revealing disturbed emotion processing in affective disorders.

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