Research report

Dissociating cognitive from affective theory of mind: A TMS study

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\textbf{A R T I C L E  I N F O}

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\textbf{A B S T R A C T}

Introduction: “Theory of Mind” (ToM), i.e., the ability to infer other persons’ mental states, is a key function of social cognition. It is increasingly recognized to form a multidimensional construct. One differentiation that has been proposed is that between cognitive and affective ToM, whose neural correlates remain to be identified. We aimed to ascertain the possible role of the right dorsolateral prefrontal cortex (DLPFC) for cognitive ToM as opposed to affective ToM processes.

Methods: 1 Hz repetitive transcranial magnetic stimulation (rTMS) was used to interfere offline with cortical function of the right DLPFC in healthy male subjects who subsequently had to perform a computerized task assessing cognitive and affective ToM.

Results: RTMS over the right DLPFC induced a selective effect on cognitive but not affective ToM. More specifically, a significant acceleration of reaction times in cognitive ToM compared to affective ToM and control items was observed in the experimental (right DLPFC) compared to the control (vertex) rTMS stimulation condition.

Conclusions: Our findings provide evidence for the functional independence of cognitive from affective ToM. Furthermore, they point to an important role of the right DLPFC within neural networks mediating cognitive ToM. Possible underlying mechanisms of the acceleration of cognitive ToM processing under rTMS are discussed.

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1. Introduction

Theory of mind (ToM) is defined as the ability to attribute mental states, such as desires, intentions and beliefs, to other people in order to explain and predict their behavior (Frith and Frith, 1999). It constitutes a central aspect of social cognition which is regarded to be a highly specialized, human-specific skill that forms a crucial prerequisite to function in social groups (Adolphs, 2003a, 2003c; Herrmann et al., 2007). ToM is commonly regarded to be mediated by a complex neural network including the medial prefrontal cortex (mPFC), the superior temporal sulcus region, the temporal pole (Frith and Frith, 2003; Siegal and Vary, 2002), and the amygdaleae (Adolphs, 2003b). Many lesion studies (e.g., Eslinger et al., 2007; Griffin et al., 2006; Happé et al., 1999; Siegal et al., 1996; Stuss et al., 2001; Winner et al., 1998) and functional imaging studies (e.g., Brunet et al., 2000; Gallagher et al., 2000; Sommer et al., 2007; Vogely et al., 2001) suggest that ToM and other social cognitive functions are mediated predominantly by a network lateralized to the right hemisphere, although evidence for bilateral (e.g., Vollm et al., 2006; Hynes et al., 2006) and left-sided involvement also exists (e.g., Baron-Cohen et al., 1999; Calarge et al., 2003; Channon and Crawford, 2000; Fletcher et al., 1995; Goel et al., 1995), probably depending on task type and modality (Kobayashi et al., 2007).

Recent social cognitive neuroscience has begun to define subcomponents of the complex concept we refer to as ToM. One important differentiation is that of ‘affection’ versus ‘cognitive’ ToM, although different terms have been used for these and related concepts (overview in Baron-Cohen and Wheelwright, 2004; Kalbe et al., 2007). Whereas cognitive ToM, for example assessed with so-called false belief tasks, is thought to require cognitive understanding of the difference between the speaker’s knowledge and that of the listener (knowledge about beliefs), affective ToM, for example tested with faux pas and irony tasks, is supposed to require in addition an empathic appreciation of the listener’s emotional state (knowledge about emotions) (Shamay-Tsoory et al., 2006). Brothers (1995, 1997) had postulated a unitary social ‘editor’ which is specialized for processing others’ social intentions but which could not be dissociated into ‘hot’ social cognition (i.e., processing others’ emotional expressions) and ‘cold’ social cognition (i.e., attributing and processing cognitive mental states such as beliefs). However, Eslinger et al. (1996) reported a dissociation between affective and cognitive aspects of ‘empathy’ in brain damaged patients. Furthermore, Blair (2005) and Blair and Cipolotti (2000) argued that divergent results concerning ToM dysfunctions in sociopathy may be attributed to a selective deterioration of affective social cognition (‘emotional empathy’), while individuals with autism show more difficulties with cognitive than with emotional empathy. Recently, Shamay-Tsoory and colleagues found selective deficits of affective as opposed to cognitive ToM in various patients groups (Shamay-Tsoory and Aharon-Peretz, 2007; Shamay-Tsoory et al., 2006, 2005).

Already Eslinger (1998) suggested that different regions in the prefrontal cortex may be relevant for these distinct functions, with a dorsolateral prefrontal cortex (DLPFC) system mediating cognitive empathy and the orbitofrontal cortex mediating affective empathy. Shamay-Tsoory et al. (2005) confirmed the special role of the ventromedial prefrontal cortex (VMPFC) in processing affective ToM and argued that cognitive ToM may rather involve both the VMPFC and dorsal parts of the prefrontal cortex (Shamay-Tsoory and Aharon-Peretz, 2007). Further confirmation for partially differential mechanisms in processing affective and cognitive ToM was recently provided by functional magnetic resonance imaging (fMRI) studies (Hynes et al., 2006). These studies underline the particular role of medial and orbital FFC for affective perspective taking and show involvement of dorsolateral prefrontal structures for cognitive ToM. Kobayashi et al. (2007) and Sommer et al. (2007) found involvement especially of the right-hemispheric DLPFC in false belief tasks (which can be categorized as cognitive ToM tasks).

In summary, research so far (a) suggests a distinction between affective and cognitive ToM functions and (b) point to at least partly different neural correlates mediating these two subcomponents. However, while the role of the VMPFC for affective ToM is well documented, neural substrates of cognitive ToM are less well defined but may include the DLPFC.

On the basis of the aforementioned considerations, we aimed to further examine the dissociation of cognitive and affective ToM processes. We tried to elucidate neural correlates of cognitive as opposed to affective ToM and, more specifically, to investigate the functional relevance of the DLPFC for cognitive ToM performance. For this purpose, we applied 1-Hz repetitive transcranial magnetic stimulation (rTMS) to the DLPFC of 28 male right-handed healthy subjects prior to the performance of a computer-based ToM task that has previously been used to differentially assess cognitive versus affective ToM (Shamay-Tsoory and Aharon-Peretz, 2007). Although functional imaging studies have shown somewhat contradictory results regarding laterality of ToM functions (see above) we decided to perform rTMS over the right DLPFC for the following reasons: (i) We used the “Yoni” paradigm introduced by Shamay-Tsoory and Aharon-Peretz (2007) in which ToM has to be inferred on the basis of eye gaze and facial expression. According to Sabbagh (2004), a right-hemispheric mechanism mediates the decoding of mental states based on immediate information, such as eye expression, while a left-hemispheric network is responsible for complex reasoning about mental states. It can be speculated that the right-hemispheric decoding system is utilized when performing the Yoni task (Shamay-Tsoory and Aharon-Peretz, 2007). (ii) Executive functions have been conceptualized as a “co-opted” system for ToM processing (Siegal and Vary, 2002), and recent functional imaging research points to the central role of the right DLPFC in executive working memory operations and cognitive control functions (Lie et al., 2006).

TMS is a well-established tool for inducing transient changes in brain activity non-invasively in conscious human volunteers. Over the past couple of years, the ability of actively interfering with neural processing during behavioral performance has been increasingly used for the investigation of causal brain-behavior relations in higher cognitive functions (Pascual-Leone et al., 2000; Sack and Linden, 2003). RTMS has been applied to different areas within prefrontal cortex in
order to successfully interfere with higher cognitive functions such as visual (Mottaghy et al., 2002; Oliveri et al., 2001) and spatial (Koch et al., 2005) working memory, verbal and nonverbal memory encoding (Floel et al., 2004), divided attention (Wagner et al., 2006), decision making (van’t Wout et al., 2005), or the implementation of fairness-related behavior (Knob et al., 2006a, 2006b). RTMS has been used in few studies to examine the sensorimotor side of empathy for pain (Avenanti et al., 2005, 2009). Only one rTMS study specifically addressed neural correlates of ToM using rTMS, finding both dorsolateral and temporoparietal involvement (Costa et al., 2008). However, no differentiation was made between cognitive and affective ToM.

For our study, we hypothesized dissociable effects of rTMS over the right DLPFC on ToM. More specifically, on the basis of the assumption that the DLPFC is involved in the neural basis of the theory of mind, we expected a selective effect of rTMS over the right DLPFC on cognitive but not affective ToM.

2. Methods

2.1. Sample

Twenty-eight male, right-handed subjects (mean age: 24.0, standard deviation – SD: 2.7) without neurological or psychiatric history were included in the study. All subjects had completed German high school with the highest degree (Abitur) and currently underwent higher university education in various fields but not psychology. The study protocol was approved by the local Ethics committee. All subjects signed informed consent and underwent a medical safety screening according to international safety guidelines for the use of TMS (Wassermann, 1998). Cognitive dysfunction was excluded with the cognitive screening instrument DemTect (Kalbe et al., 2004; Kessler et al., 2000), subtest 4 (reasoning) of the German intelligence test battery “Leistungsprüfsystem” (LPS 4, Horn, 1983), and the Trail Making Test A and B (TMT, Reitan, 1979; Tombaugh, 2004). Mean group scores were 17.4 (SD: 1.1) out of 18 points in the DemTect, C-scores of 7.3 (SD: 1.5) for the LPS 4, and percentiles of 4.4 (SD: 2.8) and 4.7 (SD: 2.9) for TMT subtests A and B, respectively.

2.2. ToM tasks

A German version of the “reading the mind in the eyes” test (Baron-Cohen et al., 2001) was used as a general measure of ToM abilities. To measure cognitive and affective ToM in the TMS experiment we used a German modified version of the “Yoni” task introduced by Shamay-Tsoory et al. (2006). It is based on a task previously described by Baron-Cohen and Goodhart (1994) and involves the ability to judge mental states via analysis of verbal cues, eye gaze, and facial expression. In each of the 60 items presented on a computer screen, a face named Yoni is shown in the middle with four coloured pictures in the corners showing either faces or examples of a semantic category (e.g., animals, fruits). An incomplete sentence about what image Yoni is referring to is also presented, and the subject has to judge which of the four stimuli in the corners best fills the gap of the sentence. The items can be subdivided into three types of categories with 20 items each, that is (i) cognitive ToM (cog), (ii) affective ToM (aff), and (iii) control physical condition (phy), with ten first order and ten second order items in each category (Fig. 1). While answers in the physical condition only require analysis of physical attributes of the character, choices in the cognitive and affective ToM items require mental inferences based on verbal cues (contained in the sentences), eye gaze and/or facial expression. More specifically, in the first order ToM stimuli Yoni’s mental state about one of the four images in the corners has to be inferred: Yoni is thinking of ... (cog1, German: Yoni denkt an ...), or Yoni loves ... (aff1, German: Yoni mag ...), while in the more complex second order ToM items the four stimuli in the corners consist of faces, and an inference regarding the interaction between Yoni’s and the other stimuli’s mental state is necessary. In the second order cognitive items with the sentence Yoni is thinking of the ... that ... wants (cog2, German: Yoni denkt an die ..., die ... willt), both the verbal and facial cues are neutral. In the second order affective items with the sentence Yoni loves the ... that ... loves, (German: Yoni mag die..., die ... mag) both cues are affective. The item sets of all item subcategories are comparable with regard to sentence complexity and visual complexity.

The task was programmed with the software PRESENTATION. The total task duration was 10 min and 30 sec. All items were presented in randomized order for a maximum of 10 sec during which the subjects had to answer by tapping a button on the square number keyboard on the right side of the console. The position of the answer buttons (1, 7, 9, 3) corresponded to the positions of the four stimuli in the corners of the screen. As soon as subjects answered, a plain white screen was shown until the end of the 10 sec time interval. Between these fixed time intervals a black fixation cross on a white screen was presented for .5 sec. In order to ensure comparability of reaction times (RTs), subjects always had to use the same finger (right middle or index finger) to respond and return to the starting position on button 5 in the middle of the number keyboard after each item. For all items, RTs and accuracy were registered.

Before rTMS stimulation and administration of the real TMS experiment we used a German modified version of the “Yoni” task with four explaining slides, and a training that resembled the test but with only 21 items (7 cognitive, 7 affective, and 7 physical) not included in the test.

2.3. Magnetic resonance imaging (MRI) localisation of rTMS target site

Each participant underwent a high resolution whole brain anatomical MRI scan performed on a whole body 1.5 T scanner (Achieva 1.5, Philips Medicine Systems, Best, the Netherlands). This allowed for defining the rTMS target site based on individual anatomical brain structure. To allow exact positioning of rTMS over the DLPFC, nifedipine capsules were sticky-taped over two frontal areas navigated prior to MRI scanning by two common landmark procedures for the DLPFC. The first of these two procedures determines DLPFC by detecting the “motor hot spot” for the abductor pollicis brevis muscle within the hand area of the primary motor cortex by
single pulse TMS and then moving 5 cm anterior and in parallel to the midsagittal line (George et al., 1995). The second approach uses the international 10–20 system to localize DLPFC as corresponding to F4 (Herwig et al., 2003) (see Fig. 2). The exact individual position of the DLPFC was determined at the junction of BA 8 and BA 9 caudal to the medial section of the medial frontal gyrus based on the anatomical brain scan of each participant. This prefrontal section was used because the dorsal part of the lateral prefrontal cortex is most clearly related with complex executive functions (Lie et al., 2006; Miller and Cohen, 2001; Petrides, 2005). Furthermore, this area has been found to be active during false belief reasoning which can be conceptualized as a cognitive ToM task (Sommer et al., 2007).

<table>
<thead>
<tr>
<th></th>
<th>1st order</th>
<th>2nd order</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>cognitive</strong></td>
<td><strong>cog1</strong></td>
<td><strong>cog2</strong></td>
</tr>
<tr>
<td></td>
<td>Yoni is thinking of ___</td>
<td>Yoni is thinking of the fruit that ___ wants</td>
</tr>
<tr>
<td></td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
</tr>
<tr>
<td><strong>affective</strong></td>
<td><strong>aff1</strong></td>
<td><strong>aff2</strong></td>
</tr>
<tr>
<td></td>
<td>Yoni loves ___</td>
<td>Yoni loves the fruit that ___ loves</td>
</tr>
<tr>
<td></td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
</tr>
<tr>
<td><strong>physical</strong></td>
<td><strong>phy1</strong></td>
<td><strong>phy2</strong></td>
</tr>
<tr>
<td></td>
<td>Yoni is close to ___</td>
<td>Yoni has the fruit that ___ has</td>
</tr>
<tr>
<td></td>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
</tr>
</tbody>
</table>

Fig. 1 – Item examples of the Yoni ToM task modified from Shamay-Tsoory et al. (2007) used in our TMS experiment.

Fig. 2 – a. Montreal Neurological Institute (MNI) headmesh showing the average locations of the two capsules in Talairach coordinates. Capsule 1 indicates the stimulation site as determined by the 5 cm rule ($x = 51 \pm 6$, $y = 34 \pm 11$, $z = 53 \pm 7$). Capsule 2 indicates F4, the stimulation site as determined by the 10–20 system ($x = 46 \pm 4$, $y = 49 \pm 5$, $z = 45 \pm 6$). b. Anatomical regions shown on segmentations of the MNI template.
In order to navigate the rTMS coil to the exact scalp position for stimulation of the DLPFC, the location of the DLPFC was calculated in relation to the anatomical locations proposed by each landmark procedure in three-dimensional MRI reconstruction. The final actual rTMS could either be based on one of the locations indicated by the two landmark procedures or on a different location on the scalp when both methods failed to overlie the intended cortical target site. The advantage of this approach is two-fold: first it provides a precise and individual determination of the MRI-guided rTMS target site and second it offers an empirical assessment of the accuracy and validity of the two most commonly used standard anatomical landmark approaches for localizing BA 9.

2.4. TMS protocol

A Magstim Rapid² stimulator (Magstim company, Whitland, UK), set at 100% of the individual resting motor threshold, and a 70 mm figure of eight coil were used to deliver a 15 min single train of 900 1 Hz rTMS at 100% of the motor threshold. Stimulation parameters were chosen according to the 1 Hz procedure described by Maeda et al. (2000) which has shown to result in a 10–15 min reduction of cortical excitability of the target area. For the detection of the resting motor threshold the coil was placed tangentially over the right primary motor cortex at the optimal site for the response of the left first dorsal interosseus muscle. The resting motor threshold was defined as the stimulator output intensity that evoked at least 5 out of 10 motor potentials of a minimum amplitude of 100 μV from the contralateral first dorsal interosseus muscle (mean was 58.4%, SD: 4%). Each subject received rTMS at two different locations – one at the cortical target site of right BA9, and one vertex (Cz) stimulation as control condition (Bestmann et al., 2002; Koch et al., 2006; Pascual-Leone et al., 1996). Cz was localized according to the international 10–20 system (Jasper, 1958). Concerning coil orientation, the figure eight coil was held tangentially to subjects’ cortex in the angle of motor spot localization. This corresponded roughly to an angle of 45° to midsagittal line of the subject’s cortex. Holding the coil was done manually with both hands during the entire stimulation.

2.5. Procedure

The study was conducted as a within-subject design, where half of the subjects were stimulated at the target area first, and the other half was stimulated at the control site first. The sequence of stimulation was randomly assigned to each participant. Subsequently to the first stimulation the subject was tested with the Yoni ToM task. After a 30 min inter-stimulation break the second stimulation was conducted after which again the Yoni ToM task was administered. ToM testing started immediately after stimulation. To ensure that subjects were familiar with the task so that simple learning effects during test administration under rTMS could be avoided, all subjects received an introduction and training of the Yoni task prior to the first stimulation. Furthermore, to ensure that subjects did not occupy themselves with the experiment at hand during the 30 min inter-stimulation break they had to administer a filler task during that break. For this purpose, a questionnaire (personality questionnaire NEO-FFI, Borkenau and Ostendorf, 1993) was chosen which was cognitively not demanding, did not interfere with the experiment, and had an administration time of approximately 30 min.

2.6. Statistical analysis

All statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS) version 15 for Windows (Release 15.0.0, Chicago: SPSS Inc.). After checking for statistical normal distribution of the data with the Kolmogorov–Smirnov-Test, a general linear model repeated measures analysis on the factors ToM condition (cognitive vs affective vs control physical items of the Yoni task) and rTMS stimulation condition (experimental vs control) was employed. For post-hoc testing paired samples t-tests with corrected α were used.

3. Results

3.1. General ToM abilities

In the ‘reading the mind in the eyes’ task the group reached a mean of 25.6 (SD = 2.1) points (max. score = 36) indicating age- and gender-adequate ToM abilities according to the normative data provided by Baron-Cohen et al. (2001).

3.2. TMS adverse events

Side effects that occurred due to rTMS stimulation were mild headache after stimulation in two subjects, eye or nose twitching during stimulation in 16 subjects and jaw contractions during stimulation in one subject. One candidate subject suffered a syncope during motor spot localization after application of 15 single pulses at different output intensities with a maximum of 70%. After an Electroencephalography (EEG) recording with normal results the subject was excluded from further participation.

3.3. Experimental ToM task “Yoni”: RTs

Mean RTs of the main Yoni ToM task categories for the experimental and control stimulation conditions are indicated in Table 1. Control physical items were processed significantly faster than cognitive (t = 11.223, df = 27, p < .001) and affective (t = 11.92, df = 27, p < .001) items in the experimental as well as in the control stimulation condition (t = 9.987, df = 27, p < .001 for cognitive and t = 8.739, df = 27, p < .001 for affective items). Affective items were processed significantly faster than cognitive items in the experimental condition (t = 11.920, df = 27, p < .001) and in the control condition (t = 3.700, df = 27, p < .001).

In a general linear model repeated measure analysis, the factors stimulation site (two stages: experimental vs control) and item type (three stages: cognitive vs affective vs control), and the between-subject factor order of condition (experimental – control vs control – experimental) were used, the latter of which is important to account for possible order effects. In this analysis, there was a significant main effect for stimulation site [Pillai’s Trace = .262, F(1,27) = 9.230, p = .005]
and item category [Pillai’s Trace = .853, F(2,26) = 72.603, p < .001] and a significant interaction effect between the factors item category and stimulation site [Pillai’s Trace = .258, F(2,26) = 4.337, p = .024]. However, neither the interaction stimulation site with order of condition nor the interaction item category with order of condition nor the three way interaction stimulation site with item category with order of condition were significant [Pillai’s Trace = .128, F(2,26) = 3.802, p = .062; Pillai’s Trace = .036, F(2,26) = .471, p = .630; and Pillai’s Trace = .111, F(2,26) = 1.558, p = .230, respectively]. Thus when stimulated experimentally compared to control stimulation, subjects differed significantly in their RTs between categories, and order of stimulation did not influence this rTMS effect on ToM performance.

Table 1 – Mean RTs in msec of answers to the categories of the Yoni ToM task in the two rTMS conditions.

<table>
<thead>
<tr>
<th>Category</th>
<th>Control stimulation</th>
<th>Experimental stimulation</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Mean RT (ms) (SD)</td>
<td>Mean RT (ms) (SD)</td>
<td></td>
</tr>
<tr>
<td>Cognitive items (total)</td>
<td>2908 (629)</td>
<td>2625 (587)</td>
<td>.001*</td>
</tr>
<tr>
<td>cog1</td>
<td>1989 (445)</td>
<td>1849 (431)</td>
<td>.021</td>
</tr>
<tr>
<td>cog2</td>
<td>3827 (936)</td>
<td>3402 (801)</td>
<td>.004*</td>
</tr>
<tr>
<td>Affective items (total)</td>
<td>2658 (580)</td>
<td>2565 (586)</td>
<td>.199</td>
</tr>
<tr>
<td>aff1</td>
<td>2130 (530)</td>
<td>2032 (544)</td>
<td>.330</td>
</tr>
<tr>
<td>aff2</td>
<td>3187 (699)</td>
<td>3096 (687)</td>
<td>.167</td>
</tr>
<tr>
<td>Physical items (total)</td>
<td>1997 (406)</td>
<td>1881 (415)</td>
<td>.042</td>
</tr>
<tr>
<td>phy1</td>
<td>1707 (368)</td>
<td>1655 (370)</td>
<td>.248</td>
</tr>
<tr>
<td>phy2</td>
<td>2287 (486)</td>
<td>2107 (488)</td>
<td>.028</td>
</tr>
</tbody>
</table>

*p < .05

Fig. 3 – Reaction time differences control minus experimental condition for cognitive and affective ToM items.

Fig. 4 – Reaction time differences control minus experimental condition for subcategories of cognitive, affective, and physical items.

To analyse whether RTs were stable over the duration of the task for cognitive ToM items, paired samples t-tests of the first versus the second half data were performed for each condition. No significant differences were observed for cog1, cog 2, and total cognitive ToM items indicating that there were no learning effects.

3.4. Experimental ToM task “Yoni”: accuracy

There were no incorrect answers from any subject. The mean number of misses (analyzed for all item categories) was 3.5 (SD = 3.3) in the experimental and 2.8 (SD = 2.9) in the control condition. Only four out of 28 subjects (14.3%) had no misses indicating that there was no ceiling effect in performance and that task difficulty was adequate. A general linear model repeated measures procedure for misses in the Yoni ToM task using the factors also included in the RT analysis (i.e., ToM condition and rTMS stimulation condition) showed no significant results, even though there was a trend for interaction between the factors stimulation site and item category [Pillai’s Trace = .188, F(2,26) = 3.009, p = .067]. Remarkably, within-group comparison of misses in the cog2 items in
control versus experimental condition did not show a significant difference (Wilcoxon test, \( Z = -1.447, p = .148 \)), indicating that there was no specific effect in this item subcategory that might be related to the results of the RT analysis.

4. Conclusion

The main finding of our study is that rTMS over the right DLPFC has a selective effect on cognitive but not affective ToM performance. This result is in concordance with the recently advanced view that these processes are subcomponents of the complex concept we refer to as ToM and are at least partially independent (Blair and Cipolotti, 2000; Eslinger, 1998; Eslinger et al., 1996). Evidence for a functional dissociability of the independence of cognitive and affective ToM also comes from patient studies, which show selective deterioration of affective ToM in patients with ventromedial damage (Shamay-Tsoory and Aharon-Peretz, 2007; Shamay-Tsoory et al., 2005), more pronounced dysfunction in affective than in cognitive ToM in patients with schizophrenia (Shamay-Tsoory et al., 2006), and also from psychophysiological findings (using skin conductance responses) in healthy control subjects (Kalbe et al., 2007). Furthermore, imaging studies have found partially different networks mediating cognitive and affective ToM (Hynes et al., 2006; Völlm et al., 2006). Although a side result of our study, it should be noted in this context that we found faster RTs for affective than for cognitive ToM items in both conditions – a finding that is in concordance with “Yoni” results of Shamay-Tsoory and Aharon-Peretz (2007) and also with behavioral results from a study that used cognitive and emotional ToM short stories matched in word length (Hynes et al., 2006). Albeit speculative at this point, the affective items might be easier than the cognitive items in the Yoni task since they involve an additional cue for making the decision: a smile or a frown. This may enhance ToM processing. Alternatively, the results could also reflect different mechanisms underlying cognitive and affective ToM. Referring to the two fundamentally different mechanisms that have been proposed to explain the process of mentalizing, ‘simulation theory’ posits that other people’s mental states are represented by replicating or mimicking the mental life of the other person and thus ‘slipping in the other person’s shoes’, while according to the ‘theory theory’, others’ mental states are modelled rationally by a knowledge system that is independent from one’s own mental states (Gallese and Goldman, 1998). Instead of favouring one of these mechanisms, it has been hypothesized that both of them exist and that cognitive ToM may primarily represent a cognitive process which relies on ‘theories’ of mind corresponding to the ‘theory theory’ while simulation may rather be the underlying mechanism for affective ToM (Adolphs, 2002; Adolphs et al., 2000; Heims et al., 2004; Kalbe et al., 2007; Mitchell et al., 2005; Shamay-Tsoory and Aharon-Peretz, 2007). Shamay-Tsoory et al. (2005) suggest that simulation mechanism is essential at the beginning of the persons’ affective ToM process and is further used for making inferences regarding the other persons’ affective mental states. Affective ToM processing or ‘empathy’ is regarded to rely on brain structures that develop early in ontogeny including the limbic system and might thus be mediated by more automatic and direct neural circuits as compared to cognitive mentalizing, that could pose more demands on cognitive resources (Hynes et al., 2006; Mitchell et al., 2005; Satpute and Lieberman, 2006; Singer, 2006) – and might thus be faster. In this context it seems to be relevant to consider the connections between limbic and prefrontal sections. The amygdala, which is the key structure in evaluating emotional sensory stimuli (e.g., Phelps, 2006; Phelps and LeDoux, 2005) is both directly and indirectly connected with the orbitofrontal/ventromedial part of the frontal lobe (e.g., Brand and Markowitsch, 2006). In addition, the amygdala is linked to fast automatic responses via its connections with hypothalamic nuclei and the brain stem. Amygdala activation can therefore result in fast automatic arousal (e.g., measured by skin conductance responses), which is then perceived by somatosensory cortex. Information about the emotionality of stimuli can significantly influence evaluative processes, such as decision making, ToM, and other complex function (Adolphs, 2001, 2003a, 2003b; Bechara et al., 2003; Brand et al., 2007; Damasio, 1994, 1996). This is most likely the case due to the aforementioned connections between amygdala and orbitofrontal cortex which has also been named “expanded limbic system” (Nauta, 1979). It is hypothesized that this limbic contribution to higher cognitive functions, in particular within the field of social cognition and those tasks that depend upon intuitive processes, is linked to faster reactions, as the emotional system acts fast, parallel, associative etc. (c.f.; Kahneman, 2003). This may – at least partially – explain why we found faster reactions to affective compared to cognitive ToM items. Taken together our results corroborate the notion that cognitive and affective ToM are functionally dissociable processes.

RTMS over the right DLPFC in our study induced an acceleration of RTs in cognitive ToM, not a decrease as might have been expected. Certainty about the reliability of this finding comes from the facts that (1) training effects can be excluded, as all subjects received a training before test administration so that they were customized to the task, and more importantly, RTs for cognitive ToM items were stable over the duration of the task (2) training or order effects on specific task trials or items can be excluded, as the order of the items within the Yoni task as well as the order of rTMS stimulation condition were randomized across subjects, and also given the result that there were no statistical effects for the factor order of condition in the general linear model repeated measure analysis (3) there was a statistically significant interaction effect between the factors item category (cognitive vs affective vs control items) and stimulation site (experimental vs control). This latter effect stems from a significant difference of RTs only in cognitive items between experimental and control stimulation. One possible explanation for the fact that processing of cognitive ToM items was faster after rTMS over the DLPFC is that our control stimulation has led to decreased RTs, not vice versa. However, this is unlikely, as rTMS stimulation over the vertex has been used as control stimulation in numerous studies using a wide variety of paradigms, and to the knowledge of the authors has not been shown to have any specific effect on visual exploration (e.g., Nyffeler et al., 2008) or other functions (Wiener et al., 2010; Viggiano et al., 2008). Furthermore, a decrease of RTs after vertex stimulation would not explain the differential effect on cognitive ToM as
compared to the affective ToM and control items. Thus the interpretation that RTs in response to cognitive ToM items were fastened after rTMS over the right DLPFC seems valid. One possible explanation for this result is that our stimulation protocol could have had a facilitating effect when applied over the right DLPFC and not an inhibitory one when applied over the primary motor cortex (Maeda et al., 2000). For example, Sack and Linden (2003) point out that one particular rTMS protocol can have either inhibitory or facilitatory effects depending on the cortical area where it is applied and the behavioral task to be tested. In addition, stimulation characteristics, such as intensity, distribution, depth of penetration, and accuracy, depend on factors such as scalp-cortex distance or extent and conductivity of the stimulated tissue. In support of these considerations, Dräger and co-workers found that specific language (namely picture-word verification) function was inhibited when a 1 Hz protocol with 600 pulses was conducted on Wernicke’s area and facilitated when it was used on Broca’s area (Dräger et al., 2004). Despite these constraints, Machii et al. (2006) in their recent review come to the conclusion that deducing stimulation parameters which are valid for motor areas and applying them to the study of cognitive function is the standard procedure which has shown to produce coherent results. Thus, although general questions remain regarding the effect of our specific rTMS protocol, it is definite that our stimulation protocol interfered with normal processing of ToM in the DLPFC.

Assuming that our rTMS protocol inhibited excitability of the right DLPFC, the fastening of RTs during the cognitive ToM tasks suggest that normal functioning of the right DLPFC is detrimental for performance in cognitive ToM processing. Thus inhibition of the right DLPFC must have facilitated other brain regions relevant for task performance, possibly by the mechanism of “transcallosal inhibition”. It is known that low frequency rTMS has been shown to reduce transcallosal inhibition within the motor system and may facilitate corticospinal excitability of the not stimulated motor cortex (Gilio et al., 2003; Pal et al., 2005). 1 Hz rTMS over the primary motor cortex facilitates function of the contralateral homologue by reduction of transcallosal inhibition (Kobayashi et al., 2004; Takeuchi et al., 2005). Comparable effects have also been demonstrated for higher cortical functions. For example, hampering function of the relevant left-hemispheric language areas, either by stroke or after rTMS, causes enhanced neural activation of the contralateral homotopic areas (Heiss et al., 2002; Thiel et al., 2006). Also, the processing of specific emotions such as anger or anxiety known to be lateralized can be modulated by rTMS over the right PFC (van Honk et al., 2002). Finally, low frequency rTMS stimulation of the right frontal cortex is as effective as high frequency rTMS stimulation of the left frontal cortex in patients with depression (Isenberg et al., 2005).

In context of the task under discussion inhibition of the right DLPFC by 1 Hz rTMS may have released left DLPFC from transcallosal inhibition and resulted in enhanced function within this area. This would point to a left rather than a right-hemispheric DLPFC relevance for cognitive ToM. There is evidence for involvement of the left PFC in ToM processing (e.g., Baron-Cohen et al., 1999; Calarge et al., 2003; Channon and Crawford, 2000; Fletcher et al., 1995; Gallagher et al., 2000; Goel et al., 1995). Sabbagh (2004) suggested two anatomically and functionally different ToM networks in the human cortex: a right-hemispheric one, especially in the orbitofrontal and medial temporal cortex, mediating ‘decoding mental states from outside cues’, and a left-hemispheric network, especially in the left medial frontal cortex, mediating ‘reasoning about those mental states’. Left-sided cortical involvement in ToM processing also includes lateral prefrontal structures (e.g., Baron-Cohen et al., 1999; Channon and Crawford, 2000; Sabbagh-Tsoory and Aharon-Peretz, 2007). In line with these results, Satpute and Lieberman (2006) recently proposed the framework of a ‘reflective’ system for automatic social perception (which relies on limbic/ventromedial and temporal structures and is needed to code the trait and evaluative implications of an observed behavior), as opposed to a ‘reflective’ system for controlled social perception. The latter system is supposed to be mediated, among other structures, partly by the lateral prefrontal cortex, which is known to mediate reasoning and logic, analogy, mathematical problem-solving as well as working memory and other executive functions. Satpute and Lieberman (2006) propose that this reflective system is involved when ‘symbolic computation’ is necessary in a ToM task. More precisely, the system could provide a corrective process of automatically generated hypothesis about interpretations of behavior (mediated by other structures), i.e., a ‘selection process’ (see also Leslie et al., 2004, 2005), and is needed where multiple mental perspectives have to be considered, self knowledge inhibited, and beliefs considered in relation to subsequent mental states (Bull et al., 2007).

In line with the aforementioned arguments one may speculate that rTMS induced inhibition of right DLPFC functioning may cause stronger involvement of emotional reactions to cognitive tasks compared to intact right DLPFC functions. The DLPFC is connected with other prefrontal areas (ventrolateral and orbitofrontal sections) and basal ganglia, via thalamic nuclei (Alexander and Crutcher, 1990; Alexander et al., 1990; Barbas, 2000; Brand and Markowitsch, 2008) and DLPFC functioning can inhibit orbitofrontal and limbic activation involved in social cognition and emotion processing (for a discussion of disinhibition and prefrontal cortex see Zamboni et al., 2008). Accordingly an inhibition of the right DLPFC may result in a disinhibition of orbitofrontal functioning that then facilitates solving cognitive ToM items in a more emotional and therefore faster way than usually done, at least as long as the items are not too complex and do not necessarily involve an executive component.

Although ToM and executive functions can be deteriorated independently and thus seem dissociable (e.g., Fine et al., 2001; Lough et al., 2001; Pickup, 2008; Rowe et al., 2001; Stone et al., 1998), an association between the two has frequently been shown (e.g., Channon and Crawford, 2000; Kobayashi et al., 2007; Perner and Lang, 1999; Perner et al., 2002; Sabbagh et al., 2006). It appears as if executive functions serve as a ‘co-opted’ system (next to a ‘core’ ToM system), which is necessary to succeed at least in particular variants of ToM tasks (Siegal and Varley, 2002). Cognitive ToM tasks which require attributions about the propositional attitudes such as belief, knowledge, intentions, are more likely to fall into this category than affective ToM tasks that are associated with the ability to
empathize (Shamay-Tsoory et al., 2002) and may involve implicit affect sharing (Singer, 2006) through simulation processing (Mitchell et al., 2005). We thus conclude that the DLPCF involvement in our study reflects contributions of executive functions in solving cognitive ToM items as assessed in the Yoni task. However, when right DLPCF functioning is reduced (via rTMS), integrity of the left DLPCF seems to be sufficient to deal with the executive component of the task. In addition, it might be that – in this case – an additional contribution of limbic structures (i.e., the right orbitofrontal section), which results from less inhibition by the right DLPCF, may facilitate solving the cognitive ToM items.

In summary, our study provides empirical evidence for the functional independence of cognitive and affective ToM. Furthermore, it points to an important role of the DLPCF within neural networks mediating cognitive ToM. However, the exact role of this region within networks mediating ToM needs to be specified. Future studies are warranted to assess functional and effective brain connectivity between left and right DLPCF during the execution of cognitive versus affective ToM tasks. More concretely, fMRI connectivity studies (Friston et al., 2003; Goebel et al., 2003) might reveal the exact neuro-computational mechanisms within bilateral DLPCF during cognitive versus affective ToM, on the bases of which optimized rTMS protocols could be applied over left versus right DLPCF in order to further elicit the relevance of this region for cognitive ToM processes.

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