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10 **Modulating functional and dysfunctional mentalizing by transcranial magnetic stimulation**

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Abstract

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Mentalizing, the ability to attribute mental states to others and oneself, is a cognitive function with high relevance for social interactions. Recent neuroscientific research has increasingly contributed to attempts to decompose this complex social cognitive function into constituting neurocognitive building blocks. Additionally, clinical research that focuses on social cognition to find links between impaired social functioning and neurophysiological deviations has accumulated evidence that mentalizing is affected in most psychiatric disorders. Recently, both lines of research have started to employ transcranial magnetic stimulation: the first to modulate mentalizing in order to specify its neurocognitive components, the latter to treat impaired mentalizing in clinical conditions. This review integrates findings of these two different approaches to draw a more detailed picture of the neurocognitive basis of mentalizing and its deviations in psychiatric disorders. Moreover, we evaluate the effectiveness of hitherto employed stimulation techniques and protocols, paradigms and outcome measures. Based on this overview we highlight new directions for future research on the neurocognitive basis of functional and dysfunctional social cognition.

Keywords: transcranial magnetic stimulation, social cognition, mentalizing, Theory of Mind, autism spectrum disorders, major depressive disorder, psychiatric disorders

1. Introduction

In the middle of the night your neighbor is desperately trying to open your door with his key. Why is he doing that and how will you react? Knowing that he just came back from a birthday party and being aware of his drinking habits, you are able to infer that he probably falsely believes it is his door he is trying to open. Instead of calling the police you might then help him to find his own apartment. This example illustrates how our ability to understand other people's behavior, by attributing mental states like beliefs, desires or intentions, also known as Theory of Mind (ToM) reasoning or mentalizing, drives social interactions.

A fast growing body of evidence suggests that mentalizing is affected in most psychiatric disorders, including but not limited to major depressive disorder (MDD; see Schreiter et al., 2013), bipolar disorder (Bora et al., 2005; Van Rheenen & Rossell, 2013), social anxiety (Ribeiro & Fearon, 2010; Samson et al., 2012), borderline personality disorder (Ghiassi et al., 2010; Mier et al., 2013); eating disorders (Schulte-Rüther et al., 2012) and neurodegenerative diseases (Le Bouc et al., 2012; Poletti et al., 2013). Moreover, it has long been hypothesized that social cognitive deficits in autism spectrum disorders (ASD) and schizophrenia result from impaired mentalizing (Brüne & Brühne-Cohrs, 2006; Frith, 2012).

However, this research is still in an early stage. Inconclusive findings (e.g., Arntz et al., 2009; Schreiter et al., 2013) and a heterogeneous conceptualization of impaired social cognition do not yet allow for drawing firm conclusions about the role of impaired mentalizing in psychiatric disorders. To resolve this ambiguity, it has been suggested to focus on the neurocognitive building blocks of mentalizing in order to find links between symptomatic impairment of social interactions and neurophysiological deviations in psychiatric disorders (Frith, 2012; Frith & Happé, 2014; Kennedy & Adolphs, 2012).

Recently, cognitive neuroscientists started to specify these neurocognitive building blocks of mentalizing using transcranial magnetic stimulation (TMS, Hétu et al., 2012). A coil, placed on the skull over the brain area of interest, produces a focal magnetic field which passes through the skull largely undistorted and induces neuronal depolarization in superficial cortical areas. When TMS is applied over specific brain regions in the context of a cognitive task, the interference with behavioral performance enables the study of causal relations between brain activity, cognitive processes, and behavior (Paus, 2005; Robertson et al., 2003; Walsh & Cowey, 2000).

TMS studies on mentalizing almost exclusively use repetitive TMS (rTMS), which is why the current review focuses on this method. A detailed description of recent technical and methodological issues for the application of various TMS protocols in the study of cognition is provided elsewhere (Sandrini et al., 2011). Applying rTMS has both an immediate interrupting effect on neuronal processing in the stimulated area, and a modulatory after-effect, which outlasts the stimulation period by minutes to hours (cf., Eisenegger et al., 2008). The direction of this after-effect (inhibitory/excitatory) depends on stimulation parameters and baseline activity of the stimulated area. Accordingly, rTMS can be applied during the performance of a cognitive task (online) or before task performance (offline). A third possibility is the application of single pulses which interrupt neuronal

1 activity for a short but well-defined period, useful for identifying temporal characteristics of
2 neurocognitive processes.

3
4 Moreover, clinical research began to employ TMS to treat impaired mentalizing in
5 psychiatric disorders. For this purpose, repeated sessions of rTMS have been applied over
6 periods of several weeks for the treatment of mentalizing deficits in ASD and MDD (Berlim et
7 al., 2012; Enticott et al., 2011; 2014).

8
9 Here, we integrate and evaluate findings of these separately emerging lines of
10 research to show how TMS can advance our understanding of the neurocognitive basis of
11 mentalizing and its impairment in clinical conditions, specifically in ASD and MDD. Further,
12 table 1 provides methodological details of hitherto available brain stimulation studies on
13 mentalizing. We suggest that TMS combined with sensitive experimental paradigms is a
14 promising method to specify the neurocognitive architecture of functional and dysfunctional
15 mentalizing, which can be the key to elucidate impaired social functioning in psychiatric
16 disorders.

17 **2. What TMS reveals about mentalizing**

18 **2.1 The neurocognitive basis of mentalizing**

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22 Based on a large corpus of findings about the neurophysiological basis of mentalizing
23 (e.g., Mar, 2011; van Overwalle, 2009), neuroscientific methods are increasingly employed
24 to test specific hypotheses about the neurocognitive processes that constitute mentalizing.
25 Here, we focus on brain regions that appear to be central for mentalizing and have been
26 targeted in TMS studies thus far, namely the temporoparietal junction (TPJ), the dorsolateral
27 prefrontal cortex (DLPFC), the inferior frontal gyrus (IFG) and the medial prefrontal cortex
28 (MPFC; Figure 1).

29 **2.1.1 Right TPJ and mental models of self and other**

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31
32 Consistently observed in neuroimaging studies on mentalizing, but little understood,
33 is functional activity of the right TPJ (RTPJ)¹. Costa et al. (2008) were the first to show that
34 stimulation of the RTPJ interferes with mentalizing. Applying 1Hz-rTMS impaired subjects'
35 performance in a false belief task (questions on stories describing false beliefs about an
36 object's location) and in a Faux Pas Test (questions on stories describing protagonists'
37 mental states that led to awkward behavior). Consistently, Giardina et al. (2011) and Young
38 et al. (2010) found that 1Hz(/10Hz-online)-rTMS over the RTPJ influenced the use of mental
39 states in reasoning about ethical or unethical behavior of others.

40
41 Crucially, TMS can not only tell us that the RTPJ is involved in mentalizing, it also
42 advances our understanding of its underlying function. As outlined below, recent TMS
43 studies provide converging evidence for the idea that RTPJ's function in mentalizing is to
44 handle internal models of one's own and other's mental states and their relation to the
45 environment (Decety & Sommerville, 2003).

46

1 Several lines of evidence from neuroimaging and brain stimulation in single cases
2 suggested that the RTPJ integrates multisensory input with internally stored information to
3 form a first-person perspective, i.e. a coherent sense of one's own body situated in and
4 distinguishable from the rest of the world (cf., Blanke et al., 2005; de Ridder et al. 2007;
5 Ionta et al., 2011). This notion has been supported by a study in which RTPJ activity has been
6 disrupted by single-pulse TMS during the rubber hand illusion, resulting in an impaired
7 ability to distinguish between self-relevant ("this is part of my body") and self-irrelevant
8 ("this is not part of my body") sensory information (Tsakiris et al. 2011). It was concluded
9 that the RTPJ maintains an internal model of one's own body as a reference for self-
10 relevance evaluations of incoming sensory information.

11
12 Heinisch et al. (2011; cf., Heinisch et al., 2012) provided evidence that the RTPJ is also
13 involved in distinguishing self-relevant from other-relevant information. In this study
14 subjects were presented with a picture of another person's face that morphed gradually into
15 a picture of their own face or vice versa. The participants indicated the moment they
16 recognized their own face, and the moment they were sure that they were seeing the face
17 of another person, respectively. The application of 1Hz-rTMS over the RTPJ biased this self-
18 other discrimination towards self-face recognition at the expense of other-face recognition.
19 Further evidence comes from a control-of-imitation task, in which the participants moved a
20 finger either congruently or incongruently to a simultaneously observed finger movement of
21 another person. The ability to control the tendency to imitate the other's movement was
22 impaired by 10-Hz-online-rTMS (Sowden & Catmur, 2013)².

23
24 In sum, these findings confirm the role of the RTPJ in mentalizing and specify that the
25 RTPJ is critically relevant for simultaneously maintaining mental models of the self and
26 others and their relation to the environment ("how do I perceive the world vs. how does the
27 other perceive the world?"). This may be achieved by integrating sensory information from
28 the environment with internally stored information (Cabeza et al., 2012) and with
29 expectations and predictions about self and other (Koster-Hale & Saxe, 2013). By this we are
30 able to flexibly switch between perspectives, depending on what is required in a certain
31 situation.

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33 **2.1.2 DLPFC, IFG and perspective inhibition**

34

35 Evidence on the role of the DLPFC in mentalizing is still too sparse to draw firm
36 conclusions about its neurocognitive role in mentalizing (cf., Costa et al., 2008; Kalbe et al.,
37 2010). Further, only little TMS research has focused on the more ventral IFG, a region with
38 much larger evidence on its involvement in mentalizing (Mar, 2011). It has been proposed
39 that the IFG's role in mentalizing is perspective inhibition (Ramsey et al., 2013; Ruby &
40 Decety, 2004). For example, when adopting another's perspective, one's own perspective
41 has to be inhibited and vice versa. While the RTPJ maintains mental models of one's own
42 and another's perspective, the IFG inhibits one of these models during perspective selection.
43 To our knowledge only one study investigated the effect of rTMS over the left IFG (Keuken et
44 al., 2011). In this study a relatively short 1Hz-rTMS of 5 minutes had no effect on
45 subsequent performance in two standard mentalizing tasks as compared to control
46 stimulation. More studies employing well-suited tasks and stimulation protocols are
47 required to test the IFG's causal role in mentalizing.

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2.1.3 MPFC and decoupling

It was proposed that the MPFC's role in mentalizing is to subserve the decoupling mechanism, i.e. processing another's perspective independently from one's own view on the world (Döhnell et al., 2012; Gallagher & Frith, 2003; Frith & Frith, 2003; Leslie, 1987, 1994). Recent neuroimaging findings showed that during the computation of one's own and another's perspective, the posterior MPFC (pMPFC) is involved in establishing a perspective difference through inhibitory influence on temporoparietal brain regions (Schuwerk et al., 2014a). It seems that while the RTPJ maintains mental models of self and other by integrating internal (memory-based/predicted) and external (sensory) information, inhibitory influence of the pMPFC suppresses processing of external information to enable the decoupled computation of one's own and another's perspective. Consistent with this idea, inhibiting the pMPFC by 1Hz-rTMS with a double-cone coil impaired the participant's ability to distinguish between one's own and another's perspective in a false belief task (Schuwerk et al., 2014b). In another study, 1Hz-stimulation of the pMPFC with so-called "deep rTMS" modulated affective ToM performance in dependence of baseline empathic abilities (Krause et al., 2012). Taken together, these findings indicate that the pMPFC can be targeted by specific rTMS techniques and encourage future rTMS research focusing on that area.

2.2 TMS to study and treat dysfunctional mentalizing?

Recently, researchers began to test the therapeutic use of [high-frequency](#) rTMS on dysfunctional mentalizing in ASD and MDD. However, little is known about specifically impaired underlying neurocognitive mechanisms: ASD is characterized by widespread structural and functional brain abnormalities (Müller et al., 2013; Philip et al., 2012). Among these, a reduced functional connectivity between the MPFC and RTPJ during mentalizing has been observed in individuals with ASD (Castelli et al., 2002; Kana et al., 2009). It can be hypothesized that the decoupled processing of one's own and another's perspective, mediated by inhibitory influence of the pMPFC to the temporoparietal cortex, is impaired in ASD. This is supported by the specific difficulty to attribute false beliefs to other people (Baron-Cohen et al., 1985; Senju et al., 2009), and close to the early hypothesis that a "failure of decoupling" underlies ASD (Leslie, 1987). If this were the case, could [high-frequency](#) stimulation of the pMPFC alleviate this mentalizing deficit?

In a double-blind randomized sham-controlled trial, Enticott and colleagues (2014) tested if [high-frequency](#) rTMS over the pMPFC improves impaired social functioning in ASD. Participants with high-functioning autism and Asperger's syndrome received 5Hz-rTMS of the pMPFC on consecutive days over about two weeks. After active treatment as compared to sham treatment, patients reported reduced social relating impairments and anxiety in social situations (Enticott et al., 2014), as well as improved social functioning, including an increased capacity for perspective taking and empathy (Enticott et al., 2011).

Taken together, this fits with the hypothesis that the mentalizing deficit in ASD is related to impaired inhibitory influence of the pMPFC on the RTPJ. However, to provide direct evidence for this idea, future TMS studies have to show that (1) [high-frequency](#) TMS

1 increases the connectivity between the pMPFC and RTPJ during mentalizing and (2)
2 improves the ability to establish a perspective difference in a sensitive experimental task.

3
4 Clinical research indicates that a mentalizing deficit also plays a role in MDD
5 (Schreiter et al., 2013). Compared to non-depressed controls, individuals with a current
6 depressive episode showed a weaker performance in decoding mental states from facial
7 expressions (Lee et al., 2005). Patients with a currently remitted MDD were impaired in a
8 second-order false belief task (inferring thoughts about thoughts; Inoue et al., 2004) and had
9 a higher risk for relapse one year later (Inoue et al., 2006). Also mentalizing-associated brain
10 regions show abnormal functional activity and connectivity in depression (aan het Rot et al.,
11 2009; Price & Drevets, 2012).

12
13 Is the neurocognitive basis of mentalizing affected in MDD? A prominent symptom of
14 depressed patients is a high self-focus, i.e. a high attentional focus on oneself compared to
15 others (e.g., Flory et al., 2000). An impaired ability to efficiently switch between one's own
16 and another's perspective might be one contributing factor to this predominant self-focus.
17 One's own negatively biased perspective constitutes the reference-point not only in
18 judgments of one's own current and future situation, but also affects how one perceives the
19 rest of the world (cf. the negative triad; Beck, 1972).

20
21 Presently, this idea remains speculative. Although a large body of evidence suggests
22 that rTMS to the DLPFC has an antidepressant effect (Lefaucheur et al., 2014), we currently
23 lack evidence on possible links between impaired neurocognitive components of mentalizing
24 and depressive symptoms. To our knowledge, only one study has addressed this issue and
25 found a relation between 10Hz-rTMS to the left DLPFC, improved performance in a ToM
26 task, and the alleviation of depressive symptoms (Berlim et al., 2012). However, these
27 preliminary findings do not allow for firm conclusions about causal associations of these
28 factors.

29
30 In sum, TMS seems to be a valuable tool in the investigation of the relationship
31 between impaired mentalizing, its neuronal correlates, and related psychiatric disorders. At
32 the same time it is definitely premature to claim that TMS constitutes a therapeutic strategy
33 to improve impaired mentalizing. But in the light of accumulating evidence that brain
34 stimulation may enhance (1) cognitive functioning in psychiatric disorders (Demirtas-
35 Tatlidede et al., 2013) and (2) mentalizing in healthy subjects (Santiesteban et al., 2012), it
36 can be regarded as a promising method to tackle dysfunctional mentalizing.

37 38 **3. Effectiveness of employed stimulation methods**

39
40 All previously employed stimulation techniques (online and offline rTMS, tDCS,
41 single-pulse TMS), brain site localization procedures, and most stimulation protocols
42 produced effects of interest (Table 1). Unfortunately, only half of the TMS studies on
43 mentalizing reviewed here reported effect sizes. In these studies the effect sizes are medium
44 to large. To improve the evaluation of observed findings and facilitate the design of future
45 studies, comprehensive descriptions of all methodological aspects and detailed reporting of
46 results, including effect sizes, are highly desirable.

47

1 A critical issue appears to be the employment of sensitive experimental paradigms.
2 Particularly, adaptations of traditional ToM tests, such as the Reading the Mind in the Eyes
3 Test (Baron-Cohen et al., 2001), ToM cartoons (Brunet et al., 2000) or social animations (e.g.,
4 Abell, Happé & Frith, 2000), produced heterogeneous results. Several authors stated that
5 their employed tasks might not be sensitive enough to measure TMS-induced effects on
6 behavioral outcome measures (e.g., Enticott et al., 2014; Krause et al., 2012; c.f., Keuken et
7 al., 2011; Lev-Ran et al., 2011). Future studies must carefully design paradigms that allow for
8 detecting TMS effects on reaction times and accuracy rates, the two most prominent
9 outcome measures.

10

11 The development of sensitive mentalizing tasks for TMS research will also be critical
12 for the evaluation of rTMS as a therapeutic approach for dysfunctional mentalizing. In a
13 review on the role of social cognition in MDD, Schreier et al. (2013) pointed out that
14 especially objective measures, i.e. laboratory tasks, seem to be more reliable and sensitive
15 than self-reports, for example.

16

Table 1
Methodological details and key findings of available TMS studies on mentalizing sorted by targeted brain region

Study	Brain region	Technique	Targeting procedure	Stimulation and Control	Paradigm	Outcome measure	Effect size*	Key findings
RTPJ								
Costa et al. (2008)	LTPJ; RTPJ	rTMS	Neuronavigation to a priori defined coordinates	1Hz, 15 min, 90% RMT; sham	Short stories: false belief/faux pas/control	PCR; RT	n/a	rTMS over RTPJ impaired performance in false belief task and in faux pas test
Giardina et al. (2011)	LTPJ; RTPJ	rTMS	Neuronavigation to a priori defined coordinates	1Hz, 600 stimuli, 90% RMT; control (10/20 EEG position Oz)	Social interaction scenarios requiring either hostile or non-hostile intentionality attributions	Number of respective intentionality attribution responses; RT	n/a	rTMS over RTPJ increased hostile intention interpretations and decreased non-hostile intention interpretations; rTMS over LTPJ tended to show the reverse pattern
Kelly et al. (2014)	LTPJ; RTPJ	Single-pulse TMS	fMRI-guided neuronavigation	70% MSO; control (2cm ant. to stimulation site)	Social attribution task: attribution of awareness to others (fMRI experiment); Visual detection task (subsequent TMS experiment)	Degree of awareness; PCR	n/a	single-pulse TMS over LTPJ/RTPJ associated with attribution of awareness to others disrupted subjects' attribution of awareness to themselves
Silani et al. (2013)	rSMG**	rTMS	MRI-guided neuronavigation	1Hz, 15 min, 110% RMT; Control (vertex); (between subj. design)	Judgments of pleasantness of self- or other-experienced visuo-tactile stimulation	Stimulation pleasantness rating	$\eta_p^2 = .098$	rTMS increased egocentric empathic judgments
Sowden & Catmur (2013)	RTPJ	online rTMS	MRI-guided neuronavigation	10Hz, 6 pulses, 110% RMT; control (mid-occipital)	Imitation-inhibition task: inhibition of other-imitation;	RT; percent error	$\eta_p^2 = .25$	rTMS decreased imitation inhibition tendency
Young et al. (2010)	RTPJ	rTMS; online rTMS (Exp.2)	fMRI-guided neuronavigation	1Hz, 25 min, 70% MSO (Exp.2: 10 Hz, 500 ms, 60% MSO); control (5cm post. to RTPJ)	Moral scenarios manipulating protagonists' beliefs and action outcomes	moral judgments; RT	$\eta_p^2 = 0.5$ 0-0.56	rTMS disrupted participants' mentalizing in moral judgments, especially when actions had the goal to harm others
MPFC								
Enticott et al. (2011)	bilateral dmPFC	rTMS	7cm anterior to M1 along the midline	5Hz, 30 10s rTMS trains (20s inter-train interval), 100% RMT; 9 sessions in 11 days	Interpersonal Reactivity Index: self-report measure of empathy; Autism Spectrum Quotient: self-report measure of autistic traits; Ritvo Autism Asperger Diagnostic Scale; Non-standardized interviews	Self-report: pre, post, 1 MO, 6 MO follow up	n/a	high-frequency rTMS lessened autistic symptoms and symptom intensity and improved social functioning in a 20-year-old woman with Asperger's syndrome
Enticott et al. (2013)	bilateral dmPFC	rTMS	7cm anterior to M1 along the midline	5Hz, 30 10s rTMS trains (20s inter-train interval), 100% RMT; Sham; (between subj./double-blind design) 10 sessions every consecutive weekday	Interpersonal Reactivity Index: self-report measure of empathy; Autism Spectrum Quotient: self-report measure of autistic traits; Ritvo Autism Asperger Diagnostic Scale; Non-standardized interviews; Reading the mind in the eyes test: decoding of mental states from facial expressions; Frith-Happé-animations:	Self-report: pre, post, 1 MO follow up; PCR; Amount and appropriateness of mentalizing	Cohen's $d = 0.41-1.41$	high-frequency rTMS (compared to sham stimulation) reduced social relating impairments and anxiety in social situations in individuals with Asperger's syndrome or high-functioning autism; No effects on experimental tasks

					mental state attribution to geometric shapes;			
Krause et al. (2012)	bilateral dmPFC	rTMS	7cm anterior to M1 along the midline	1Hz, 15min, 100% RMT; Sham	Yoni task: cognitive and affective mentalizing; Reading the mind in the eyes test: decoding of mental states from facial expressions	PCR; RT	Cohen's $d=0.66-0.81$	rTMS reduced affective ToM performance in subjects with high self-reported empathy and increased affective ToM performance in subjects with low self-reported empathy
Lev-Ran et al. (2012)	Ventromedial MPFC	rTMS	MRI-guided neuronavigation (based on scans from 3 subjects) to BA11,12	1Hz, 100 stimuli before each of 4 subtests, 100% RMT (of right foot); Sham (to a superior temporal region); (between subj. design)	Yoni task: affective mentalizing, judgment of character's gaze direction	RT	n/a	rTMS affected learning mechanisms in the affective mentalizing task
Schuwerk et al. (2014b)	pMPFC	rTMS	1.5cm anterior to 1/3 of the distance from nasion toinion	1Hz; 33 min, 100% RMT; sham	False belief task requiring the computation of another's and one's own belief	PCR; RT	$\eta_p^2 = .24$	rTMS impaired the ability to distinguish the other's from one's own perspective
DLPFC/IFG								
Berlim et al. (2012)	IDLPFC	rTMS	10/20 EEG position F3	10Hz, 75 4s rTMS trains (26s inter-train interval); 120% RMT; daily for 4 weeks	Reading the mind in the eyes test: decoding of mental states from facial expressions; HaM-d ₂₁ (Hamilton 1960): clinician-rated measure of major depression intensity	PCR; Rating scores	n/a	Performance in Reading the mind in the eyes test improved in proportion to major depression symptoms improvement
Costa et al. (2008)	IDLPFC; rDLPFC;	rTMS	Neuronavigation to a priori defined coordinates	1Hz, 15 min, 90% RMT; sham	Short stories: false belief/faux pas/control	PCR; RT	n/a	rTMS over rDLPFC impaired performance in false belief task; rTMS over rDLPFC and IDLPFC impaired performance in faux pas test
Kalbe et al. (2010)	rDLPFC	rTMS	MRI-guided neuronavigation, combined with 10/20 EEG position F4 and 5cm-rule	1Hz, 15 min; 100% RMT; control (vertex)	Yoni task: cognitive and affective mentalizing	PCR; RT	n/a	rTMS over rDLPFC accelerated RTs in cognitive mentalizing and had no effect on affective mentalizing
Keuken et al. (2011)	lIFG	rTMS	10/20 EEG position F7	1Hz, 5 min; 45% MSO; control (vertex, 10/20 EEG position Cz); (between subj. design)	Modification of the Reading the mind in the eyes test: decoding of mental states from facial expressions; Modification of cartoon task (Brunet et al., 2000): attribution of belief and intentions; reasoning about physical causations	PCR; RT	n/a	No effect of rTMS on task performance

Notes: RTPJ, right temporoparietal junction; LTPJ, left temporoparietal junction; rTMS, repetitive transcranial magnetic stimulation; RMT, resting motor threshold; RT, reaction time; PCR, percentage of correct responses; (f)MRI, (functional) magnetic resonance imaging; MSO, maximum stimulator output; rSMG, right supramarginal gyrus; dmPFC, dorsomedial PFC; M1, primary motor cortex; BA, Brodmann area; MPFC, medial prefrontal cortex; (r/l)DLPFC (right/left) dorsolateral PFC, lIFG, left inferior frontal gyrus;

* effect size of statistical analysis/analyses which was/were central for the interpretation of TMS effects

** the rSMG as targeted in this study is anterior to the RTPJ

4. Future directions and conclusions

To date, available TMS studies on mentalizing show that the RTPJ, DLPFC and MPFC, identified by previous neuroimaging research on ToM, are causally involved in mentalizing. Given the correlational nature of functional magnetic resonance imaging or electroencephalography, this is a critical finding that adds to neuropsychological evidence on the causal role of those brain regions in ToM (e.g., Samson & Michel, 2013). Further, TMS is particularly suited to specify the neurocognitive building blocks of mentalizing, a current issue in ToM research. A major challenge for future research will be to develop sensitive paradigms to detect TMS-induced effects on mentalizing.

Future research should focus on the connectivity between mentalizing-associated brain regions. Both brain functions and stimulation effects are not restricted to specific regions, but have to be conceptualized as network effects. Only if we understand the brain as a network can we learn more about how the interplay of its regions underpins functional and dysfunctional social cognition (e.g., Kennedy & Adolphs, 2012). Although a set of brain regions, which were linked to mentalizing by previous research, is labeled “ToM network”, little is known about the critical interactions of those regions. One avenue for future research will be the simultaneous stimulation of several brain regions associated with mentalizing while another approach is the combination of brain stimulation and neuroimaging for the assessment of stimulation-induced network effects.

Claiming that TMS can be used as a therapeutic intervention for dysfunctional mentalizing is clearly premature. But, preliminary evidence for its influence on mentalizing in ASD and MDD promises that TMS, combined with sensitive paradigms, will provide insights into the dysfunction of the neurocognitive basis of mentalizing in clinical conditions. In the future, it may be possible to combine TMS with psychotherapeutic interventions in order to tackle impaired social cognition in psychiatric disorders.

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- 11

1 **Figure Legend**

2

3 **Figure 1.** Schematic overview of brain regions that have been targeted by non-invasive brain
4 stimulation to study functional and dysfunctional mentalizing. Color labels are approximate.
5 *A.* Sagittal view of the brain showing the posterior medial prefrontal cortex (pmPFC,
6 indicated in light-blue) and the ventromedial prefrontal cortex (vmPFC, in green). *B.* Lateral
7 view of the left (L) hemisphere of the brain. Colored regions display the left inferior frontal
8 gyrus (IFG; in dark-blue), the left dorsolateral prefrontal cortex (DLPFC; in yellow), and the
9 left temporoparietal junction (LTPJ; in purple). *C.* Lateral view of the right (R) hemisphere:
10 the right DLPFC is displayed in yellow, the right temporoparietal junction (RTPJ) in purple.

11

12 **Footnotes**

13 ¹Also the left TPJ is involved in mentalizing (e.g. Samson et al., 2004; Schurz et al., 2013).
14 However, because recent theoretical discussions focus on the RTPJ and the TMS studies
15 reviewed here also predominantly targeted the RTPJ, we concentrate on this region in
16 the current article.

17

18 ²A similar effect was previously shown by Santiesteban et al. (2012) using the same task
19 but a different stimulation method, namely transcranial direct current stimulation.
20 Intriguingly, anodal tDCS (which increases cortical excitability) enhanced the ability to
21 control imitation. Moreover, Santiesteban and colleagues showed that anodal tDCS not
22 only facilitated the self at the expense of the other, but also vice versa. In another task,
23 anodal stimulation facilitated the subjects' ability to inhibit their own perspective in
24 order to adopt the perspective of another person. We point at this finding because of its
25 high theoretical relevance. However, it is difficult to directly compare tDCS and rTMS
26 findings as those two methods substantially differ. We refrain from a detailed discussion
27 of this tDCS study as this falls beyond the scope of this review. For a general overview of
28 both noninvasive brain stimulation methods see Wagner et al. (2007).

Figure 1.JPEG

