The effects of repetitive transcranial magnetic stimulation on empathy: A systematic review and meta-analysis

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Abstract

Empathy is a multi-dimensional concept with affective and cognitive components, the latter often referred to as Theory of Mind (ToM). Impaired empathy is prevalent in people with neuropsychiatric disorders, such as personality disorder, psychopathy, and schizophrenia, highlighting the need to develop therapeutic interventions to address this. Repetitive transcranial magnetic stimulation (rTMS), a non-invasive therapeutic technique that has been effective in treating various neuropsychiatric conditions, can be potentially used to modulate empathy. To our knowledge, no systematic reviews or meta-analyses in this field have been conducted. The aim of the current study was to review the literature on the use of rTMS to modulate empathy in adults. Seven electronic databases (AMED, Cochrane library, Embase, Medline, Pubmed, PsycInfo, and Web of Science) were searched using appropriate search terms. Twenty-two studies were identified, all bar one study involved interventions in healthy rather than clinical populations, and 18 of them, providing results for 24 trials, were included in the meta-analyses. Results showed an overall small, but statistically significant, effect in favour of active rTMS in healthy individuals. Differential effects across cognitive and affective ToM were evident. Subgroup analyses for cognitive ToM revealed significant effect sizes on excitatory rTMS, offline paradigms, and non-randomised design trials. Subgroup analyses for affective ToM revealed significant effect sizes on excitatory rTMS, offline paradigms, and non-randomised design trials. Meta-regression revealed no significant sources of heterogeneity. In conclusion, rTMS may have discernible effects on different components of empathy. Further research is required to examine the effects of rTMS on empathy in clinical and non-clinical populations, using appropriate empathy tasks and rTMS protocols.

The effects of repetitive transcranial magnetic stimulation on empathy: A systematic review and meta-analysis

Successful human socialisation is heavily influenced by the abilities to detect and understand cognitive and emotional processes in others. These abilities are referred to as the Theory of Mind (ToM) and empathy (Gallese, 2003; Young *et al.*, 2010; Keuken *et al.*, 2011; Krall *et al.*, 2016). Clinicians and researchers use these terms interchangeably, but there is no universal consensus on their definitions and constructs. For example, some authors regard empathy as a two-component construct with affective and cognitive components (e.g., Reniers *et al.*, 2011) whilst others (e.g., Blair, 2005) have proposed a three-component construct by adding a motor component to reflect the act of mirroring the motor responses of the observed person (motor empathy). Some commentators view cognitive empathy as synonym to ToM which is the ability to attribute mental states, such as desires, intentions and beliefs, to others (Frith & Frith, 1999). Some authors have favoured a ToM model with two distinct components, namely affective and cognitive (e.g., Kalbe *et al.*, 2010). Others have suggested that empathy and ToM encompass similar underlying abilities that are discernible at the neural level (e.g., Reniers *et al.*, 2014). More recently, Dvash & Shamay-Tsoory (2014) argued in favour of a two-component construct of empathy, namely emotional and cognitive empathy (also refered to as ToM), with distinct neuroanatomical underpinnings (Fig.1). According to this model cognitive empathy (ToM) has two distinct subcomponents, namely affective ToM and cognitive ToM.

Several brain regions have been implicated in cognitive ToM, including medial prefrontal cortex (mPFC), dorsolateral prefrontal cortex (DLPFC), temporoparietal junction (TPJ) and temporal poles (Frith & Frith, 1999; Völlm *et al.*, 2006; Carrington & Bailey, 2009; Reniers *et al.*, 2014). Brain areas implicated in the regulation of affective ToM include mPFC, particularly the ventral portion (Shamay-Tsoory & Aharon-Peretz, 2007; Shamay-Tsoory *et al.*, 2009; Sebastian *et al.*, 2012), inferior frontal gyrus (IFG), anterior cingulate cortex, and amygdala (Shamay-Tsoory *et al.*, 2009; Gonzalez-Liencres *et al.*, 2013; Gentili *et al.*, 2015).

Self-report inventories commonly used to measure empathy include the Hogan Empathy Scale (Hogan, 1969), the Interpersonal Reactivity Index (IRI; Egger *et al.*, 1997), the Balanced Emotional Empathy Scale (BEES; Mehrabian, 2000), the Empathy Quotient (EQ; Behan *et al.*, 2015), and the Questionnaire of Cognitive and Affective Empathy (QCAE; Reniers *et al.*, 2011). Behavioural measures of cognitive empathy (ToM) are primarily performance-based and include such tasks as first-order (Baron-Cohen *et al.*, 1985) and second-order false-belief (Baron-Cohen, 1989) tasks for assessing cognitive ToM, the Reading the Mind in the Eyes (RMET) for evaluating affective ToM (Baron-Cohen *et al.*, 2001), and the Faux Pas Recognition (FPR) test (Stone *et al.*, 1998) and the Yoni task (Shamay-Tsoory & Aharon-Peretz, 2007) for assessing both affective and cognitive ToM.

Impairment of social functioning consequent upon impaired empathy has been reported in a range of neuropsychiatric conditions, including psychopathy, antisocial personality disorder (Dolan & Fullam, 2004), schizophrenia (Bragado-Jimenez & Taylor, 2012), major depressive disorder (MDD; Schreiter *et al.*, 2013), autistic spectrum disorder (ASD; Shimoni *et al.*, 2012), temporal lobe epilepsy (Li *et al.*, 2013), Alzheimer's disease (Laisney *et al.*, 2013), Parkinson's disease (Yu *et al.*, 2012), and other neurodegenerative diseases (Poletti *et al.*, 2012). Empathy is highly correlated with violence (Jolliffe & Farrington, 2004) and plays a pivotal role in the violence inhibition system (Blair *et al.*, 2005). Thus, enhancement of empathy has been regarded as a major treatment goal in criminogenic programmes (Day *et al.*, 2010; Reidy *et al.*, 2013). However, conventional psychological interventions for empathy enhancement have proved less effective in certain offender groups, particularly those with psychopathy (Reidy *et al.*, 2013), highlighting the need to develop alternative therapeutic interventions to enhance empathy, of which transcranial magnetic stimulation (TMS), especially its repetitive format (rTMS), is an example (Glenn & Raine, 2008; Glannon, 2014).

TMS is a non-invasive technique used to deliver brief, high-intensity magnetic pulses to the brain inducing localised neuronal depolarization to regulate cortical excitability that underlies the modulation of cortical networks (Luber & Lisanby, 2014). In general, high frequency (≥ 5 Hz) rTMS and its newer version, intermittent theta burst stimulation (iTBS), facilitate cortical excitability, whereas low frequency (about 1 Hz) rTMS and continuous theta burst stimulation (cTBS) contribute to opposite effects (Pascual-Leone *et al.*, 2000; Huang *et al.*, 2005; Wassermann & Zimmermann, 2012). rTMS has been used to treat a variety of neurological and psychiatric diseases (see Wassermann & Zimmermann, 2012) and to enhance cognitive functions in healthy volunteers (see Hsu *et al.*, 2015) and in people with MDD (Serafini *et al.*, 2015). Table S1 provides more information about the effects of TMS in clinical populations. Additionally, rTMS has been used to modulate empathy with some promising effects (see Hetu *et al.*, 2012; Schuwerk *et al.*, 2014a). However, findings are inconsistent likely due to differences in the tasks used to measure empathy, experimental designs, targeted brain regions, and rTMS parameters, including the paradigms used (i.e., online or offline), stimulus intensity (measured as a percentage of resting motor threshold [rMT] or of maximum stimulator output [MSO]), frequency and number of pulses.

We therefore aimed to conduct a systematic review and meta-analysis of the literature on the effects of rTMS on empathy in healthy and clinical populations to integrate the evidence base and to determine if certain TMS parameters or brain regions selected are associated with stronger effects on specific domains of empathy. Whilst effective interventions involving healthy individuals could potentially be extended to clinical populations, as we shall describe later in this review, all the studies included in this review, bar one study, involved interventions in in healthy groups. Due to the overlaps between the concepts of empathy and ToM, in this review we have conceptualised empathy in accordance with the model proposed by Dvash & Shamay-Tsoory (2014) as outlined above. We followed PRISMA-P guidelines (Moher *et al.*, 2015; Shamseer *et al.*, 2015) in the reporting of this review where applicable.

Method

Data sources

Using the terms ”transcranial magnetic stimulation” or ”TMS“ combined with “theory of mind”, “ToM”, “empath$”, “mentali$”, “role taking”, or “perspective taking”, a systematic search of the literature on the effects of TMS on empathy was conducted on 25 May 2016 of seven electronic databases (AMED, Cochrane library, Embase, Medline, PsycInfo, Pubmed, Web of Science). The International Clinical Trials Registry Platform (World Health Organization), Dissertation Abstracts, Google, and the library catalogues of the University of Nottingham were also searched to identify grey literature in the field. No filters were added regarding the age of study participants, publication time or language of publication (see online supplement Table S2 for search syntax). References of eligible articles were searched manually for potentially eligible studies missed by the electronic searches.

Study selection

Empirical studies were included in the review if they: (1) involved adult participants without dementia or other major neurological conditions; (2) used rTMS as an active intervention; (3) had a comparison group or control condition; and (4) used behavioural tasks to assess empathy. Of the 508 papers originally identified, 22 met the inclusion criteria (see Fig. S1 and Table S3) and were quality assessed using the quality assessment tool for quantitative studies (National Collaborating Centre for Methods and Tools, 2008) on the domains of selection bias, study design, confounders, blinding, data collection method, withdrawals and dropouts, intervention integrity, and statistical analyses.

Of the 22 studies included in the review, four (Uddin *et al.*, 2006; Balconi *et al.*, 2010; Hoekert *et al.*, 2010; Lev-Ran *et al.*, 2012) were excluded from the meta-analyses due to lack of sufficient data to allow effect size calculation and only after exhausting attempts to obtain this information from the authors.

Data extraction and analyses

A standardised form was used to extract information concerning authors, study objectives, sample characteristics, inclusion/exclusion criteria, study design, experimental processes, rTMS protocols, outcome variables, and analytic strategy.

We originally intended to conduct separate meta-analyses of studies involving clinical populations and healthy individuals using the random-effects model and, where applicable, in accordance with the model proposed by Dvash & Shamay-Tsoory (2014) with its components: cognitive empathy (i.e., ToM, including cognitive ToM and affective ToM) and affective empathy. However, this has not been possible due to there being only one study in the field (Enticott et al, 2014). Therefore, the meta-analyses presented in this review include only studies involving healthy subjects. Measures of cognitive ToM included the cognitive component of the Yoni task, moral judgement, false-belief tasks, and action-understanding tools. Measures of affective ToM included the RMET, tasks of facial expression recognition, the affective component of the Yoni task, affective go/no-go tasks, the faux pas test and emotional egocentricity. While it can be argued that facial expression recognition is not a test of empathic abilities, the model proposed by Dvash & Shamay-Tsoory (2014) regards emotional recognition as a component of affective ToM. This view has been supported by other commentators (e.g., Poletti et al. 2012), Therefore, tasks measuring emotional recognition, such as facial expression recognition taks, were included in the review.

Effect size was regarded as positive if the active rTMS effect was in the predicted direction and negative if it was in the opposite direction. Moreover, when a study entailed multiple stimulation sites, each trial of the different stimulation sites was used as the unit of analysis for the purpose of meta-analysis. A pooled effect size was used if a study provided multiple outcomes (e.g., accuracy and reaction time, score of each subscale, or short-term and long-term performance). Only the comparison between experimental and sham group (condition) was selected when a trial consisted of more than one control group or condition (e.g., one group receiving rTMS at a control site and another receiving sham stimulation). Effect sizes represented as Hedges' *g* and 95% confident intervals (CI) were calculated according to the differences between experimental (real stimulation) and control (sham stimulation) conditions in post-stimulation evaluations or "online" performance divided by pooled standard deviation.

The Q and I^2 statistics (Higgins & Thompson, 2002; Higgins *et al.*, 2003) were used to assess consistency between studies. The Q statistic represents the level of heterogeneity while the I^2 index specifies the total variation from between-study variance. A P value ≤ .05 and an I^2 value of greater than 40% were deemed as indicative of moderate heterogeneity. Funnel plots (Egger & Smith, 1995), the Egger test (Egger *et al.*, 1997), and Begg and Mazumdar rank correlation tests (Begg & Mazumdar, 1994) were used to test for the presence of a potential publication bias.

In cases where publication bias was evident, the Trim and Fill procedure (Egger & Smith, 1995) was applied to correct it.

In order to identify variables which could contribute to alternation of empathy, pre-specified subgroup analyses were performed with the unit of trial by merging the data according to the rTMS parameters, including effect (“excitatory” vs. “inhibitory”), stimulation paradigm (“online” vs. “offline”), study design (“randomised” vs. “non-randomised”), stimulation site and task of outcome measurement.

Meta-regression was employed to examine the impact of between-study variation on study effect sizes. The effect size from each trial was set as the dependent variable while age, gender, intensity of stimulation, total pulses per condition, and weighted number of pulses (i.e., total number of rTMS pulses multiplied by intensity) were selected as predictor variables. All the quantitative analyses were performed using Stata 13.1 (StataCorp, 2013).

Results

Study characteristics

Table 1 summaries study characteristics. In summary, 22 studies involving 466 participants (82% males; mean age: 24.45 years; range: 18-59 years) were included in the review. For studies recruiting participants from clinical populations, there was only one study (Enticott *et al.*, 2014), recruiting patients with ASD as subjects. Sixteen of the included studies were conducted in Europe, three in North America (Uddin *et al.*, 2006; Young *et al.*, 2010; Keuken *et al.*, 2011), two in Australia (Krause *et al.*, 2012; Enticott *et al.*, 2014) and one in Israel (Lev-Ran *et al.*, 2012). The most common study design employed was non-randomised crossover (*n* = 15), allocating the sequence of intervention conditions with counterbalancing (*n* = 10) or unspecified (*n* = 5) method. Of the six studies randomly allocating participants, two (Keuken *et al.*, 2011; Enticott *et al.*, 2014) were parallel randomised controlled trials and the other four (Costa *et al.*, 2008; Kalbe *et al.*, 2010; Giardina *et al.*, 2011; Lev-Ran *et al.*, 2012) were randomised crossover trials. The remaining one between-subject study (Silani *et al.*, 2013) did not mention the method of participant allocation.

Various tasks were used to assess empathy, including facial expression recognition tasks with materials derived from Ekman & Friesen (1976), the RMET or its modified version, the Yoni task, scenarios using video clips assessing individuals' capability of social judgement or action-understanding, the false belief task and the faux pas task. With regard to published self-report instruments, only one study (Enticott *et al.*, 2014) selected a self-report measure, the IRI, as the empathy measure. The number of pulses within each experimental session ranged from 120 to 3000. The majority of the reviewed studies (*n* = 15) set the intensity of the pulses to 100% or more of rMT, while other four studies used subthreshold intensity (Costa *et al.*, 2008; Hoekert *et al.*, 2010; Giardina *et al.*, 2011; Michael *et al.*, 2014). The remaining three studies (Young *et al.*, 2010; Keuken *et al.*, 2011; Krall *et al.*, 2016) selected MSO as the index of intensity. The DLPFC, mPFC (ventral or dorsal portion), TPJ, and IFG were targeted as the main sites for stimulation. The most common control condition was vertex stimulation (*n* = 11). Five studies did not report the detail of their sham protocol.

Quality assessment

Of the twenty-two studies included, only one study (Enticott *et al.*, 2014) attracted a rating of “strong”, nineteen studies were rated as “moderate”, and two studies as “weak” (Table S4). Poor rating on selection bias was the most common reason for not reaching the “strong” quality threshold. The two weak ratings were due to vulnerability to confounders (Silani *et al.*, 2013) and poor description of the reliability and validity of the outcome measures used (Michael *et al.*, 2014). For rTMS reproducibility, most of the reviewed studies (*n* = 16) provided all necessary parameters, but two studies (Balconi *et al.*, 2010; Silani *et al.*, 2013) failed to provide information in relation to the type of coil utilised and four studies (Pobric & Hamilton, 2006; Costa *et al.*, 2008; Balconi *et al.*, 2011; Balconi & Bortolotti, 2012) lacked comprehensive information about the duration of the intervention. Only three studies described adverse effects relating to the administration of rTMS, with one study indicating no adverse effects observed (Young *et al.*, 2010) and the other two studies reporting minor post-rTMS side effects (Enticott *et al.*, 2014) and one syncope event (Kalbe *et al.*, 2010).

Meta-analysis

Effects of rTMS on empathy in clinical populations

Since there was only one trial (Enticott *et al.*, 2014) involving participants with a mental disorder it was not possible to conduct a meta-analysis to examine the rTMS effect on empathy in clinical populations. This study (Enticott *et al.*, 2014) showed that deep high frequency rTMS applied bilaterally to the dorsal mPFC in patients with ASD did not have a statistically significant facilitatory effects on empathy (g = -0.22; 95% CI, -1.55 to -0.01, p = 0.016), cognitive empathy (g = -0.32; 95% CI, -1.07 to 0.44, p = 0.41), or affective empathy (g = 0.08; 95% CI, -0.66 to 0.82, p = 0.21).

Effects of rTMS on empathy in healthy volunteers

Twenty-four trials extracted from reports of 17 studies were included for the meta-analysis of the effects of rTMS on empathy. This revealed a significant small overall effect size (g = 0.29; 95% CI, 0.10 to 0.48, p = 0.003) as plotted in Fig. 2a. A moderate level of heterogeneity was observed across the studies (Q_{23} = 39.22, p = .019; I^2 = 41.4%). Separate meta-analyses were conducted for trials involving cognitive empathy with its two components; cognitive and affective ToM. However, it was not possible to conduct a meta-analysis on the effects of rTMS on affective empathy due to lack of studies in the field.

Effects of rTMS on cognitive ToM

The meta-analysis of findings from 16 trials on the effects of rTMS on cognitive ToM showed a non-significant mean effect (g = 0.12, 95% CI, -0.15 to 0.40, p = .39; see also Fig. 2b). The trim and fill procedure applied suggested an estimated mean effect size of -0.13 after imputing five missing trials (Fig. S2b). A moderate heterogeneity was found across trials (Q_{16} = 30.64, p = .01; I^2 = 51.0%). The funnel plot was asymmetrical by visual inspection (Fig. S2a), but neither the Begg's test (z = 0.95, p = .34) nor the Egger's test (intercept$_{16}$ = 2.42, t = 1.18, 2-tailed p = .26) suggested publication bias.

The subgroup analyses (Table 2) revealed a non-significant mean effect for inhibitory rTMS (g = 0.03, 95% CI, -0.27 to 0.33, p = .83) but a significant one for excitatory rTMS (g = 0.58, 95% CI, 0.05 to 1.10, p = .03). For the stimulation paradigm, since all trials with offline paradigms applied inhibitory rTMS and all trials with online paradigms applied excitatory rTMS, the results of the subgroup analysis were the same (offline: g = 0.03, 95% CI, -0.27 to 0.33, p = .83; online: g = 0.58, 95% CI, 0.05 to 1.10, p = .03). Moreover, the subgroup analysis for study designs revealed a non-significant mean effect size for trials with randomised design (g = -0.16, 95% CI, -0.56 to 0.25, p = .45) but a significant one for trials with non-randomised design (g = 0.40, 95% CI, 0.13 to 0.67, p = .004). Furthermore, the subgroup analysis for stimulation sites revealed non-significant mean effect sizes for all stimulation sites, including TPJ (g = 0.26, 95% CI, -0.04 to 0.56, p = .09), DLPFC (including IFG) (g = -0.09, 95% CI, -0.71 to 0.53, p = .79) and mPFC (g = 0.04, 95% CI, -0.44 to 0.52, p = .87). Finally, the subgroup analysis for the nature of outcome measure tasks revealed non-significant mean effect sizes for false-belief tasks (g = 0.10, 95% CI, -0.21 to 0.41, p = .51) and intention attribution tasks (g = -0.10, 95% CI, -0.57 to 0.37, p = .69) but a significant large mean effect size for action-understanding tasks (g = 0.82, 95% CI, 0.34 to 1.30, p = .001).

The meta-regression analysis across trials showed that none of between-study variables significantly predicted the effects of rTMS (mean age of participants: β = 0.08, p = .55; gender ratio: β = -1.01, p = .11; intensity of stimulation: β = -0.03, p = .26; number of pulses per condition: β = -0.005, p = .45; weighted number of pulses: β = 0.005, p = .48).

Effects of rTMS on affective ToM

The meta-analysis of results from 15 trials on the effects of rTMS on affective ToM showed a significant small mean effect (g = 0.26, 95% CI, 0.02 to 0.50, p = .03) with a moderate heterogeneity (Q_{14} = 25.98, p = .03; I^2 = 46.1%; see also fig. 2c). The funnel plot (Fig. S3a) and the Egger's test ($intercept_{17}$ = -4.39, t = -2.55, 2-tailed p = .02) showed evidence of publication bias However, the Begg's test (z = 1.48, p = .14) and the trim and fill procedure did not show evidence of publication bias.

Further subgroup analyses showed that the mean effect size of inhibitory rTMS trials failed to reach statistical significance (g = 0.25, 95% CI, -0.00 to 0.51, p = .052). It was not possible to calculate the mean effect size for excitatory rTMS since there was only one trial (Balconi & Canavesio, 2013) in this subgroup which showed a positive effect (g = 0.33). For stimulation paradigms, trials with “offline” paradigms revealed a non-significant mean effect (g = 0.10, 95% CI, -0.12 to 0.32, p = .35) while trials with “online” paradigm showed a significant moderate effect (g = 0.52, 95% CI, 0.05 to 1.00, p = .03). The subgroup analysis for study design revealed a non-significant mean effect size for trials with randomised design (g = -0.06, 95% CI, -0.36 to 0.24, p = .71) but a significant one for trials with non-randomised design (g = 0.43, 95% CI, 0.123 to 0.73, p = .006). Regarding the sites of stimulation, all three locations revealed non-significant mean effect sizes (TPJ: g = -0.14, 95% CI, -0.74 to 0.46, p = .65; DLPFC [including IFG]: g = 0.28, 95% CI, -0.35 to 0.91, p = .39; mPFC: g = 0.22, 95% CI, -0.07 to 0.52, p = .14). For type of measurement, the mean effect sizes for trials using emotion recognition tasks (g = 0.32, 95% CI, -0.06 to 0.69, p = .10) and faux-pas recognition tasks (g = -0.08, 95% CI, -0.50 to 0.35, p = .73) were not significant.

The meta-regression analysis across trials showed that none of between-study variables significantly predicted the effects of rTMS (mean age of participants: β = 0.07, p = .44; gender ratio: β = -0.68, p = .22; intensity of stimulation: β = 0.15, p = .07; number of pulses per condition: β = 0.02, p = .11; weighted number of pulses: β = -0.02, p = .11).

Discussion

This study aimed to examine the literature on the effects of rTMS on empathy and, where relevant, to determine which intervention parameters were associated with stronger effects. Our findings show that rTMS has a significant but small overall effect on empathy in healthy participants and that this effect varied according to empathy domains, cognitive or affective ToM. It has not been possible to draw valid conclusions regarding the effect of rTMS on empathy in clinical population as there was only one study conducted in the field.

The meta-analysis of rTMS studies relating to cognitive ToM revealed a non-significant effect size indicating that rTMS may not be effective in modulating cognitive ToM. Moreover, the results suggested that there might be five unpublished trials investigating this issue with negative findings. In contrast, a significant effect size was found on the meta-analysis of rTMS studies for affective ToM though the magnitude of effect was small. These findings of dissimilar effects of rTMS support the idea of examining subcomponents of empathy separately as they are associated with distinct brain regions (Dvash & Shamay-Tsoory, 2014).

Our subgroup analyses further identified parameters associated with a positive effect of rTMS, including excitatory vs. inhibitory rTMS and online vs. offline paradigms. However, these finding should be interpreted with caution due to the relatively small number of trials, particularly for excitatory rTMS. Although previous studies (e.g., Robertson *et al.*, 2003) suggest that the duration of the rTMS after-effect only persists for half of the stimulation time, physiological evidence indicates that the rTMS aftereffect decays gradually with time (Eisenegger *et al.*, 2008). Nevertheless, given that completion of conventional tasks measuring empathy is time-consuming, it is less likely to detect significant rTMS effect on empathy from experiments with offline paradigm.

Surprisingly, the subgroup analysis by stimulation site did not reveal statistically significantmean effects across different brain regions pertaining to specific empathetic components. The literature suggests differential roles of specific brain regions: The dorsal part of mPFC and TPJ (particularly the right side) for cognitive ToM (e.g., Denny *et al.*, 2012) and the ventral part of mPFC and IFG for affective ToM (Sebastian *et al.*, 2012; Dal Monte *et al.*, 2014). It would thus be expected to find significant effects if rTMS is administered to these regions, but not to other regions. However, we found no significant effect applying rTMS to TPJ for cognitive ToMor IFG for affective ToM and only one included trial (Keuken *et al.*, 2011) explored affective ToM targeting at these crucial regions (e.g., IFG), a firm conclusion cannot be drawn at this stage. It is worth noting here that t*he issue of spatial resolution is an inherent limitation of TMS research. The issue may be further compromised when* non- imaging guided techniques are utilised to localise the stimulation sites. With this in mind, and since *a* considerable number of studies included in this review (e.g., Balconi *et al.*, 2010; Balconi & Bortolotti, 2012; Krause *et al.*, 2012; Schuwerk *et al.*, 2014) did not utilise imaging guided techniques, *we have categorised the studies according to the effects of TMS on relatively large regions of the brain rather than smaller ones while performing subgroup analyses. Nevertheless,* the results need to be interpreted with caution.

Meta-regression revealed no differential effects in relation to participant characteristics (age, gender) or stimulation parameters (intensity, number of pulses, weighted number of pulses). This may be due to the low heterogeneity detected in relation to participants' age and gender ratio. Contrary to the findings of other meta-analytic studies (e.g., Chou *et al.*, 2015), rTMS parameters did not contribute significantly to effect sizes. A number of explanations exists as to why these findings were not replicated in this review. First, the number of studies included in this review was slightly higher than 10, the minimum number required to attain sufficient statistical power (Borenstein *et al.*, 2009). Second, the impact of the rTMS parameters may only be evident when rTMS is applied to the brain region corresponding to the task measured. Third, empathy is a multifaceted construct involving a network of brain regions, and since the effects of TMS are dose-dependent, a larger number of sessions and pulses per session may be required to modulate empathy.

Future research should examine a number of pertinent issues. For example, some of the included studies (Balconi & Bortolotti, 2013; Balconi & Canavesio, 2016) suggested that baseline level of empathy can moderate the inhibitory effect of low frequency rTMS on facial emotional recognition. Interestingly, they found people with higher levels of empathy performed better under control conditions than those with lower levels of empathy when the activity of the dorsal mPFC was inhibited. However, for the effect of facilitatory rTMS for enhancing empathetic ability, the role of baseline empathy level has not yet been investigated which is obviously a crucial issue for rTMS in clinical application. In addition, as speculated in a number of included studies, the behavioural tasks selected might not be appropriate for outcome measures due to their low sensitivity to detect rTMS-induced effects (e.g.,Keuken *et al.*, 2011; Krause *et al.*, 2012; Lev-Ran *et al.*, 2012; Enticott *et al.*, 2014; Schuwerk *et al.*, 2014b). Finally, it might be too simplistic to expect that increased excitability contributes to behavioural improvement and decreased excitability to a deterioration as others have also suggested (Sandrini *et al.*, 2011).

Strengths and limitations

A major strength of this study is that some of the studies included were relatively well designed with low dropouts rates and high reproducibility of rTMS protocols. However, the study suffered a number of limitations in relation to selection bias, reflected by restricted participants' age range, recruitment resources and reporting adverse of effects which is essential in TMS studies (Rossi *et al.*, 2009). Further, the subgroup analysis of study design showed that more significant effects were found in non-randomised than randomised trials. This raises the question whether the results of the current study may be vulnerable to some methodological limitations. However, since a majority of included studies were rated as equivalently moderate in quality assessment, the source of heterogeneity is less likely from allocation bias and needs further investigation. While the research on rTMS application into alteration of empathy is still in its infancy, this systematic review with meta-analysis applied a broad range of search terms to enrol eligible studies with variant outcome measures and different rTMS protocols. We included both randomised and non-randomised trials as a considerable number of studies in this field used non-randomised design. Multiple databases were thoroughly searched to minimise potential publication bias. However, a number of studies could not be included in the meta-analysis due to not reporting effect sizes, outcome measures not matching our inclusion criteria and the presence of possible publication bias. The majority of included studies applied empathy tasks providing multiple outcomes, such as accuracy and reaction time. We dealt with these multiple outcomes by averaging the effect sizes though this may have underestimated the size of effect. The number of studies included in the meta-analysis is relatively small, and this in conjunction with considerable levels of heterogeneity across the studies may have affected the power of the study. Finally, only one study involving interventions in a clinical population was included in the review and no meta-analytic data could therefore be provided for clinical samples. This highlights the urgent need to conduct clinical trials in the field.

Conclusion

The present review with meta-analysis demonstrated that rTMS has a discernible contribution to the alteration in different components of empathy although the effect sizes may not be as favourable as expected. The most encouraging finding for clinical implications is the effect of excitatory rTMS on enhancing *affective ToM*. Therefore, this review may help researchers having an interest in exploring rTMS impacts on empathy tailor their rTMS protocols to maximise its effect. Future studies in the field can potentially examine the effects of excitatory rTMS in clinical populations with impaired empathetic capabilities, such as those with ASD, psychopathy and schizophrenia. However, we do not currently know whether the same effects will be observed in these populations. rTMS parameters may have to be refined further to maximise the effects on crucial brain regions and there is a need to develop ecologically validated and sensitive empathy tasks for rTMS experiments.

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Conflict of interest

None.

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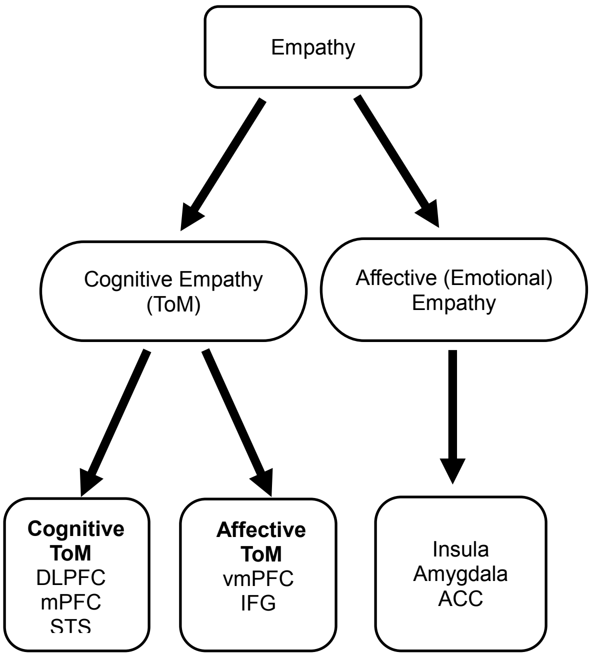
Figures Captions

Figure 1. Empathy system adapted from Dvash and Shamay-Tsoory (2014)

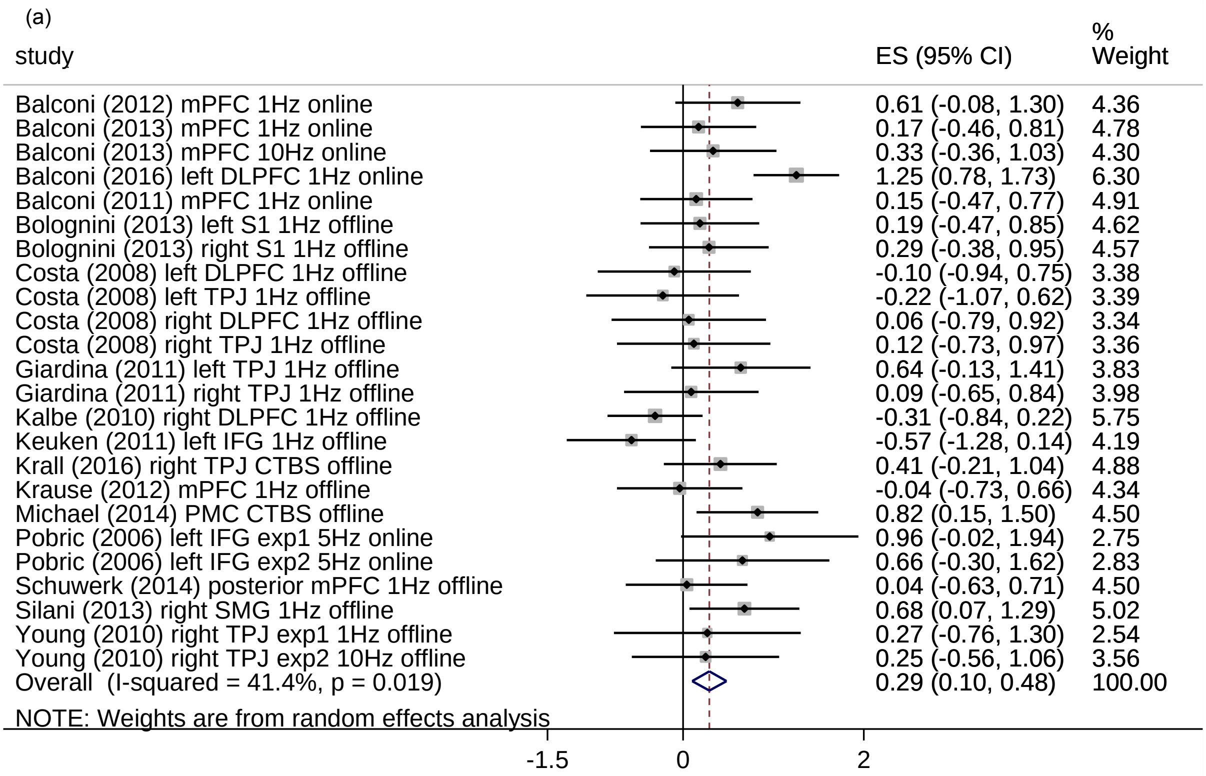
Abbreviations: ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; mPFC, medial prefrontal cortex; STS, superior temporal sulcus; ToM, Theory of Mind; TPJ, temporoparietal junction; vmPFC, ventromedial prefrontal cortex

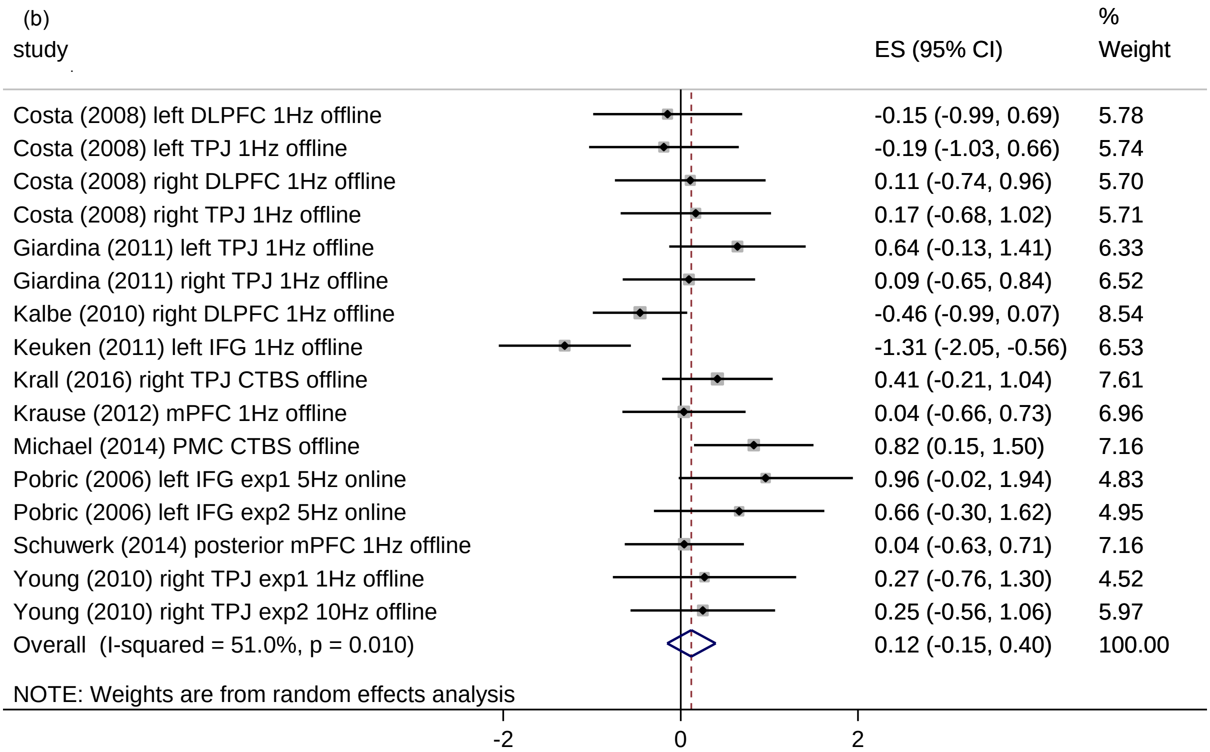
Figure 2. (a) Statistical summary and forest plot of effect sizes for empathy. **(b)** Statistical summary and forest plot of effect sizes for cognitive ToM. **(c)** Statistical summary and forest plot of effect sizes for affective ToM

Abbreviations: DLPFC, dorsolateral prefrontal cortex; ES, effect size; IFG, inferior frontal gyrus; mPFC, medial prefrontal cortex; PMC, primary motor cortex; S1, primary somatosensory area; SMG, Supramarginal gyrus; TPJ, temporoparietal junction TBS, theta burst stimulation; TPJ, temporoparietal junction



Empathy
Cognitive Empathy (ToM)
Affective (Emotional) Empathy
Cognitive ToM
DLPFC
mPFC
STS
Affective ToM
vmPFC
IFG
Insula
Amygdala
ACC


(a)
study
ES (95% CI)
% Weight
Balconi (2012) mPFC 1Hz online 0.61 (-0.08, 1.30) 4.36
Balconi (2013) mPFC 1Hz online 0.17 (-0.46, 0.81) 4.78
Balconi (2013) mPFC 10Hz online 0.33 (-0.36, 1.03) 4.30
Balconi (2016) left DLPFC 1Hz online 1.25 (0.78, 1.73) 6.30
Balconi (2011) mPFC 1Hz online 0.15 (-0.47, 0.77) 4.91
Bolognini (2013) left S1 1Hz offline 0.19 (-0.47, 0.85) 4.62
Bolognini (2013) right S1 1Hz offline 0.29 (-0.38, 0.95) 4.57
Costa (2008) left DLPFC 1Hz offline -0.10 (-0.94, 0.75) 3.38
Costa (2008) left TPJ 1Hz offline -0.22 (-1.07, 0.62) 3.39
Costa (2008) right DLPFC 1Hz offline 0.06 (-0.79, 0.92) 3.34
Costa (2008) right TPJ 1Hz offline 0.12 (-0.73, 0.97) 3.36
Giardina (2011) left TPJ 1Hz offline 0.64 (-0.13, 1.41) 3.83
Giardina (2011) right TPJ 1Hz offline 0.09 (-0.65, 0.84) 3.98
Kalbe (2010) right DLPFC 1Hz offline -0.31 (-0.84, 0.22) 5.75
Keuken (2011) left IFG 1Hz offline -0.57 (-1.28, 0.14) 4.19
Krall (2016) right TPJ CTBS offline 0.41 (-0.21, 1.04) 4.88
Krause (2012) mPFC 1Hz offline -0.04 (-0.73, 0.66) 4.34
Michael (2014) PMC CTBS offline 0.82 (0.15, 1.50) 4.50
Pobric (2006) left IFG exp1 5Hz online 0.96 (-0.02, 1.94) 2.75
Pobric (2006) left IFG exp2 5Hz online 0.66 (-0.30, 1.62) 2.83
Schuwerk (2014) posterior mPFC 1Hz offline 0.04 (-0.63, 0.71) 4.50
Silani (2013) right SMG 1Hz offline 0.68 (0.07, 1.29) 5.02
Young (2010) right TPJ exp1 1Hz offline 0.27 (-0.76, 1.30) 2.54
Young (2010) right TPJ exp2 10Hz offline 0.25 (-0.56, 1.06) 3.56
Overall (I-squared = 41.4%, p = 0.019) 0.29 (0.10, 0.48) 100.00
NOTE: Weights are from random effects analysis
-1.5
0
2


(b)
study
ES (95% CI)
% Weight
Costa (2008) left DLPFC 1Hz offline -0.15 (-0.99, 0.69) 5.78
Costa (2008) left TPJ 1Hz offline -0.19 (-1.03, 0.66) 5.74
Costa (2008) right DLPFC 1Hz offline 0.11 (-0.74, 0.96) 5.70
Costa (2008) right TPJ 1Hz offline 0.17 (-0.68, 1.02) 5.71
Giardina (2011) left TPJ 1Hz offline 0.64 (-0.13, 1.41) 6.33
Giardina (2011) right TPJ 1Hz offline 0.09 (-0.65, 0.84) 6.52
Kalbe (2010) right DLPFC 1Hz offline -0.46 (-0.99, 0.07) 8.54
Keuken (2011) left IFG 1Hz offline -1.31 (-2.05, -0.56) 6.53
Krall (2016) right TPJ CTBS offline 0.41 (-0.21, 1.04) 7.61
Krause (2012) mPFC 1Hz offline 0.04 (-0.66, 0.73) 6.96
Michael (2014) PMC CTBS offline 0.82 (0.15, 1.50) 7.16
Pobric (2006) left IFG exp1 5Hz online 0.96 (-0.02, 1.94) 4.83
Pobric (2006) left IFG exp2 5Hz online 0.66 (-0.30, 1.62) 4.95
Schuwerk (2014) posterior mPFC 1Hz offline 0.04 (-0.63, 0.71) 7.16
Young (2010) right TPJ exp1 1Hz offline 0.27 (-0.76, 1.30) 4.52
Young (2010) right TPJ exp2 10Hz offline 0.25 (-0.56, 1.06) 5.97
Overall (I-squared = 51.0%, p = 0.010) 0.12 (-0.15, 0.40) 100.00
NOTE: Weights are from random effects analysis
-2
0
2

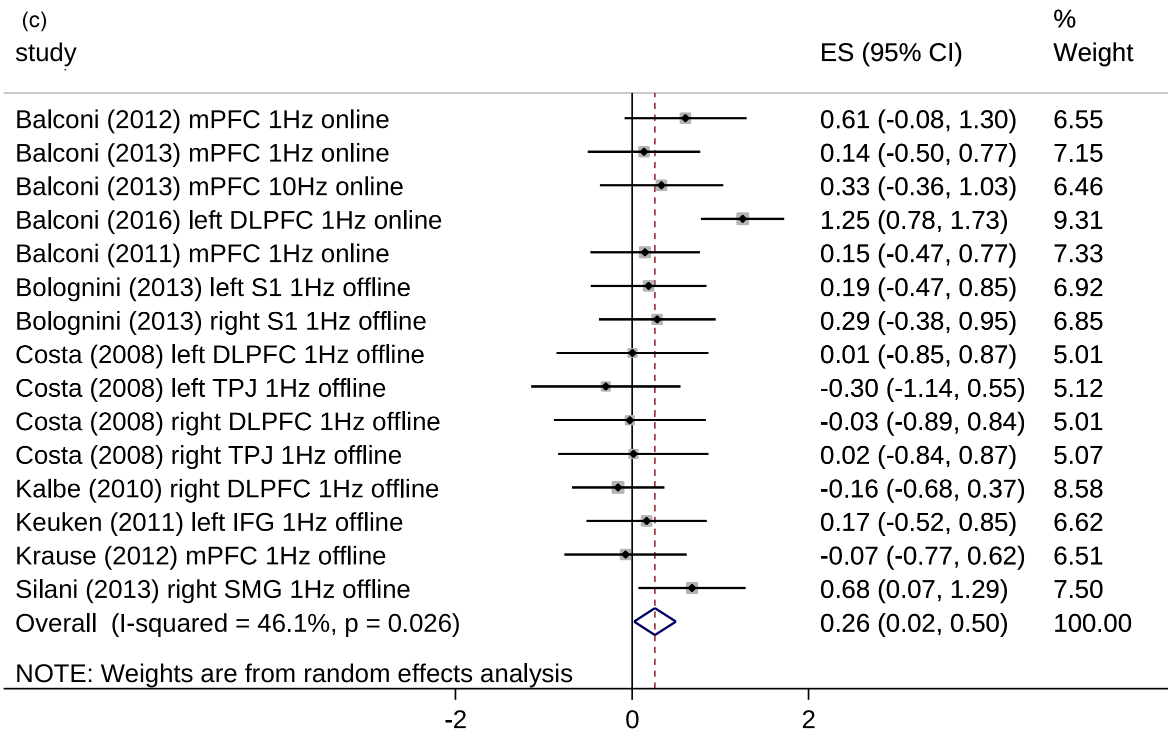

(c)
study
ES (95% CI)
%
Weight
Balconi (2012) mPFC 1Hz online 0.61 (-0.08, 1.30) 6.55
Balconi (2013) mPFC 1Hz online 0.14 (-0.50, 0.77) 7.15
Balconi (2013) mPFC 10Hz online 0.33 (-0.36, 1.03) 6.46
Balconi (2016) left DLPFC 1Hz online 1.25 (0.78, 1.73) 9.31
Balconi (2011) mPFC 1Hz online 0.15 (-0.47, 0.77) 7.33
Bolognini (2013) left S1 1Hz offline 0.19 (-0.47, 0.85) 6.92
Bolognini (2013) right S1 1Hz offline 0.29 (-0.38, 0.95) 6.85
Costa (2008) left DLPFC 1Hz offline 0.01 (-0.85, 0.87) 5.01
Costa (2008) left TPJ 1Hz offline -0.30 (-1.14, 0.55) 5.12
Costa (2008) right DLPFC 1Hz offline -0.03 (-0.89, 0.84) 5.01
Costa (2008) right TPJ 1Hz offline 0.02 (-0.84, 0.87) 5.07
Kalbe (2010) right DLPFC 1Hz offline -0.16 (-0.68, 0.37) 8.58
Keuken (2011) left IFG 1Hz offline 0.17 (-0.52, 0.85) 6.62
Krause (2012) mPFC 1Hz offline -0.07 (-0.77, 0.62) 6.51
Silani (2013) right SMG 1Hz offline 0.68 (0.07, 1.29) 7.50
Overall (I-squared = 46.1%, p = 0.026) 0.26 (0.02, 0.50) 100.00
NOTE: Weights are from random effects analysis
-2
0
2

Table 1. Characteristics of included rTMS studies on empathy

Study (country)	Study design	participants number‡, Age(Mean± SD, range), male%, Diagnosis if not healthy volunteers	Tasks	Stimulation position	rTMS protocol (frequency, intensity, stimulation, paradigm, number of pulses per condition)	Sham method
Balconi & Bortolotti, 2012 (Italy)	UCR	18, (23.40± 2.60, 20-30), 44%	Facial expression recognition	mPFC	1Hz, 120% rMT, online, 400 pulses	Vertex stimulation & unknown sham method at FCz
Balconi & Bortolotti, 2013 (Italy)	CCR	19, (23.13± 2.11, 20-30), 47%	Facial expression recognition	dorsal mPFC	1Hz, 120% rMT, online, 400 pulses	Vertex stimulation & unknown sham method at mPFC
Balconi, Bortolotti, & Gonzaga, 2011 (Italy)	UCR	20, (23.73± 2.08, 20-30), 45%	Facial expression recognition	mPFC	1Hz, 120% rMT, online, 200 pulses	Vertex stimulation & unknown sham method at mPFC
Balconi & Canavesio, 2013 (Italy)	UCR	16, (23.11± 1.93, 20-28), 38%	Facial expression recognition	mPFC	10Hz, 120% rMT, online, 2500 pulses	Vertex stimulation & tilt (45 degree) coil at mPFC
Balconi & Canavesio, 2016 (Italy)	CCR	46, (26.77± 0.17, NA), 57%	Facial expression recognition	left DLPFC	1Hz, 120% rMT, online, 400 pulses	Vertex stimulation & tilt (45 degree) coil at left DLPFC
Balconi, Crivelli, & Bortolotti, 2010[c] (Italy)	UCR	18, (23.46± 2.65, NA), NA	Facial expression recognition	ACC	1Hz, 120% rMT, online, 400 pulses	Vertex stimulation & unknown sham method at FCz
Bolognini et al., 2013 (Italy)	CCR	Exp1: 18, (22.6± 3.5, NA), 11% Exp2: 18, (24.5±3.8, NA), 17%	Affective go/no-go task	Exp1: right S1 Exp2: left S1	1Hz, 110% rMT, offline, 600 pulses	Exp1:left DLPFC stimulation & no stimulation Exp2: right DLPFC stimulation & no stimulation
Costa et al., 2008 (Italy)	RCR†	11, (22.5± 3.0, NA), 45%	Short stories: false belief/faux pas/control	left TPJ right TPJ left DLPFC right DLPFC	1Hz, 90% rMT, offline, 900 pulses	unknown sham method
Enticott et al.,	RCT	28(active: 15, sham: 13),	IRI	bilateral dorsal	5 Hz, 100% rMT, offline, 900	Sham coil

2014 (Australia)		(32.32±11.80, 18-59), 82%, ASD	RMET, Frith-Happé-animations	mPFC	pulses	
Giardina et al., 2011 (Italy)	RCR†	14, (22±3, NA), 21%	Social interaction scenarios requiring either hostile or non-hostile intentionality attributions	left TPJ right TPJ	1Hz, 90% rMT, offline, 600 pulses	Occipital cortex stimulation
Hoekert et al., 2010[c] (Netherlands)	CCR	9, (21.8± 2.6, 18-26), 40%[a]	Emotional language task	left IFG, right IFG	5Hz, 90% rMT, online, 576 pulses	right IFG stimulation Sham coil
Kalbe et al., 2010 (Germany)	RCR†	28, (24.0± 2.7, NA), 100%	RMET, Yoni task	right DLPFC	1Hz, 100% rMT, offline, 900 pulses	Vertex stimulation
Keuken et al., 2011 (USA)	RCT†	37 (active: 18, control: 19), (20.4± 2.0, 18-29), 100%	Modified RMET, Attribution of belief and intentions; reasoning about physical causations (modified from Brunet et al., 2000)	left IFG	1Hz, 45% MSO, offline, 300 pulses	Vertex stimulation
Krall et al., 2016 (Germany)	CCR	24, (27.7± 4.5, 18 – 40), 54%	False belief task	right TPJ	cTBS, 30% MSO, offline, 600 pulses	Vertex stimulation
Krause et al., 2012 (Australia)	UCR	16, (26.42± 3.82, 18 – 40), 38%	Yoni task RMET	bilateral dorsal mPFC	1 Hz, 100% rMT, offline, 900 pulses	Sham coil
Lev-Ran et al., 2012[c] (Israel)	RCR†	13, (24.73± 2.89, NA), 62%	Yoni task	ventral mPFC	1Hz, 100% rMT, offline, 400 pulses	Superior temporal region stimulation
Michael et al., 2014 (Denmark)	CCR	20, (23.5, 18–40), 60%	Action-understanding task	The hand and lip area in the left M1	cTBS, 70% rMT, offline, 300 pulses	Either stimulation site as control
Pobric and Hamilton, 2006 (UK)	CCR	exp1:9, (NA, 21-35), 64%[b] exp2:9, (NA, 21-35), 64%[b]	Action-understanding task	left IFG	5Hz, 110% rMT, online, 240 pulses	left occipital cortex stimulation, Vertex stimulation, &

						no stimulation
Schuwerk et al., 2014 (Germany)	CCR	17, (22.2± 2.3, NA), 35%	False belief task requiring the computation of another's and one's own belief	posterior mPFC	1Hz, 100% rMT, offline, 2000 pulses	Tilt (90 degree) coil at posterior mPFC
Silani et al., 2013 (Switzerland)	CCT	45 (active: 22 control: 23), (NA, NA), 0%	Judgments of pleasantness of self- or other-experienced visuo-tactile stimulation	right SMG	1Hz, 110% rMT, offline, 900 pulses	Vertex stimulation
Uddin et al., 2006[c] (USA)	CCR	8, (26.6, NA), 25%	self–other facial discrimination task	right IPL	1Hz, 100% rMT, offline, 1200	Left IPL stimulation
Young et al., 2010 (USA)	CCR	Exp1: 8, (NA, 18-30), 38% Exp2: 12, (NA, 18-30), 42%	Moral scenarios manipulating protagonists' beliefs and action outcomes	right TPJ	Exp1: 1Hz, 70% MSO, offline, 1500 pulses Exp.2: 10Hz, 60% MSO, online, 120 pulses	5 cm posterior to the right TPJ stimulation

ACC, anterior cingulate cortex; ASD, autistic spectrum disorder; CCR, counterbalanced crossover design; CCT, clinical controlled trial; cTBS, continuous theta burst stimulation; DLPFC, dorsolateral prefrontal cortex; Exp: experiment; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; IRI, Interpersonal Reactivity Index; M1, primary motor cortex; mPFC, medial prefrontal cortex; MSO, maximum of stimulator output; NA, not available; RCR, randomised crossover design; RCT, randomised controlled trial; RMET, Reading the Mind in the Eye Test; rMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation; S1, primary somatosensory area; SMG, Supramarginal gyrus; TPJ, temporoparietal junction; UCR, crossover design with unknown allocation

† no randomisation method reported

‡ presented as number of participants included in final analysis and the number of participants in subgroups in the parenthesis

[a] presented as the original sex ratio

[b] presented as the sex ratio of participants in the whole study

[c] not included for meta-analysis

Table 2. Subgroup analyses

	Pooled effect size			Between-study heterogeneity		
	k	Effect size (Hedges' *g*)	95% CI	*Q* test	I^2	*p* value
Cognitive ToM						
Total	16	0.12	-0.15-0.40	30.64	51.0%	0.010
Effect of stimulation						
Inhibitory	13	0.03	-0.27-0.33	25.66	53.2%	0.012
Excitatory	3	0.58*	0.05-1.10	1.23	0.0%	0.539
Stimulation paradigm						
Online	3	0.58*	0.05-1.10	1.23	0.0%	0.539
Off-line	13	0.03	-0.27-0.33	25.66	53.2%	0.012
Study design						
Randomised	8	-0.16	-0.56-0.25	15.83	55.8%	0.027
Non-randomised	8	0.40*	0.13-0.67	5.40	0.0%	0.611
Stimulation site						
TPJ	7	0.26	-0.04-0.56	2.50	0.0%	0.869
DLPFC (including IFG)	6	-0.09	-0.71-0.53	18.34	72.7%	0.003
mPFC	2	0.04	-0.44-0.52	0.00	0.0%	0.992
Type of used task						
False-belief	6	0.10	-0.21-0.41	1.81	0.0%	0.875
Intention attribution	7	-0.10	-0.57-0.37	16.87	64.4%	0.010
Action understanding	3	0.82*	0.34-1.30	0.18	0.0%	0.912
Affective ToM						
Total	15	0.26*	0.02-0.50	25.98	46.1%	0.026
Effect of stimulation						
Inhibitory	14	0.25	-0.00-0.51	25.97	49.9%	0.017
Excitatory	1	0.33	-0.36-1.03	-	-	-
Stimulation paradigm						
Online	5	0.52*	0.05-1.00	11.95	66.5%	0.018
Off-line	10	0.10	-0.12-0.32	6.08	0.0%	0.732
Study design						
Randomised	6	-0.06	-0.35-0.50	0.91	0.0%	0.970
Non-randomised	9	0.43*	0.12-0.73	16.71	52.1%	0.033
Stimulation site						
TPJ	2	-0.14	-0.74-0.46	0.26	0.0%	0.611
DLPFC (including IFG)	5	0.28	-0.35-0.91	19.03	79.0%	0.001
mPFC	5	0.22	-0.07-0.52	2.11	0.0%	0.716
Type of used task						
emotion recognition	8	0.32	-0.06-0.69	20.66	66.1%	0.004
faux-pas recognition	4	-0.08	-0.50-0.35	0.35	0.0%	0.950

CI, confidence interval; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; mPFC, medial prefrontal cortex; ToM, Theory of Mind; TPJ, temporoparietal junction
* $p < .05$

Online Supplementary materials

Table S1: rTMS effects in clinical populations (after Wassermann and Zimmermann, 2012)

Population	Effects
Depression	rTMS at DLPFC yields a medium to large effect size on reducing the severity of depressive symptoms.
Schizophrenia	Low-frequency rTMS significantly reduces intensity of auditory hallucinations but is less efficient in improving negative symptoms.
Obsessive compulsive disorder (OCD)	High-frequency rTMS may reduce compulsions; the finding has not been replicated consistently across studies.
Posttraumatic stress disorder (PTSD)	High-frequency rTMS may have positive and sustainable therapeutic effects on anxiety.
Parkinson's Disease (PD)	High-frequency rTMS may have beneficial effects on motor disorders
Alzheimer disease (AD)	High-frequency, offline rTMS may contribute to small short-term improvement in cognitive functioning

Table S2: Search syntax

AMED (Allied and Complementary Medicine) 1985 to May 2016		
#	**Searches**	**Results**
1	transcranial magnetic stimulation.mp.	287
2	TMS.mp.	116
3	Theory of mind.mp.	56
4	ToM.mp.	25
5	mentali*.mp.	20
6	role taking.mp.	3
7	perspective taking.mp.	5
8	empathy.mp.	343
9	1 or 2	313
10	3 or 4 or 5 or 6 or 7 or 8	429
11	**9 and 10**	**1**

Cochrane Library: Issue 4 of 12, April 2016; Cochrane Central Register of Controlled		
#	**Searches**	**Results**
#1	transcranial magnetic stimulation	2024
#2	TMS	796
#3	Theory of mind	659
#4	ToM	164
#5	mentali*	96
#6	role taking	800
#7	perspective taking	176
#8	empath*	453
#9	#1 or #2	2235
#10	#3 or #4 or #5 or #6 or #7 or #8	2233
#11	#9 and #10	6

OVID: Embase 1980 to 2016 Week 21		
#	**Searches**	**Results**
1	transcranial magnetic stimulation.mp.	18219
2	TMS.mp.	12740
3	Theory of mind.mp.	4908
4	ToM.mp.	3625
5	mentali*.mp.	3749
6	role taking.mp.	164
7	perspective taking.mp.	1354
8	empath*.mp.	23301
9	1 or 2	23283
10	3 or 4 or 5 or 6 or 7 or 8	33707
11	**9 and 10**	**128**

OVID MEDLINE(R) 1946 to May Week 2 2016		
#	**Searches**	**Results**
1	transcranial magnetic stimulation.mp.	10734
2	TMS.mp.	7672
3	Theory of mind.mp.	3010
4	ToM.mp.	2291
5	mentali*.mp.	2406
6	role taking.mp.	151
7	perspective taking.mp.	857
8	empath*.mp.	18755
9	1 or 2	13734
10	3 or 4 or 5 or 6 or 7 or 8	25376
11	**9 and 10**	**59**

OVID: PsycINFO 1806 to May Week 3 2016		
#	**Searches**	**Results**
1	transcranial magnetic stimulation.mp.	7371
2	TMS.mp.	3724
3	Theory of mind.mp.	7047
4	ToM.mp.	3343
5	mentali*.mp.	5698
6	role taking.mp.	2669
7	perspective taking.mp.	3265
8	empath*.mp.	26113
9	1 or 2	7824
10	3 or 4 or 5 or 6 or 7 or 8	42782
11	**9 and 10**	**65**

Pubmed 25052016		
#	**Searches**	**Results**
#1	Search (transcranial magnetic stimulation) OR TMS	16057
#2	Search **(((((theory of mind) OR mentali*) OR empath*) OR perspective taking) OR role taking) OR ToM**	61634
#3	Search (#1) AND #2	131

Web of Science Core Collection: Citation Indexes: Science Citation Index Expanded (SCI-EXPANDED) --1900-present; Social Sciences Citation Index (SSCI) --1956-present; Arts & Humanities Citation Index (A&HCI) --1975-present; Conference Proceedings Citation Index- Science (CPCI-S) --1990-present; Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH) --1990-

present		
#	**Searches**	**Results**
#1	"transcranial magnetic stimulation"	16137
#2	TMS	13326
#3	"Theory of mind"	5489
#4	ToM	10802
#5	mentali*	6906
#6	"role taking"	436
#7	"perspective taking"	3171
#8	empath*	18938
#9	#1 or #2	23415
#10	#3 or #4 or #5 or #6 or #7 or #8	41869
#11	#9 and #10	116

Table S3: The list of the excluded studies

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Table S4. Component and overall quality ratings of the reviewed studies

Study	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Overall
Balconi & Bortolotti, 2012	+	+++	+++	++	+++	+++	++
Balconi & Bortolotti, 2013	+	+++	+++	++	+++	+++	++
Balconi, Bortolotti, & Gonzaga, 2011	+	+++	+++	++	+++	+++	++
Balconi & Canavesio, 2013	+	+++	+++	++	+++	+++	++
Balconi & Canavesio, 2016	+	+++	+++	++	+++	+++	++
Balconi, Crivelli, & Bortolotti, 2010	+	+++	+++	++	+++	+++	++
Bolognini et al., 2013	+	+++	+++	++	+++	+++	++
Costa et al., 2008	+	+++	+++	++	+++	+++	++
Enticott et al., 2014	++	+++	+++	+++	+++	+++	+++
Giardina et al., 2011	+	+++	+++	++	+++	+++	++
Hoekert et al., 2010,	+	+++	+++	++	+++	+++	++
Kalbe et al., 2010	+	+++	+++	++	+++	+++	++
Keuken et al., 2011	+	+++	+++	++	+++	+++	++
Krause et al., 2012	+	+++	+++	++	+++	+++	++
Lev-Ran et al., 2012	+	+++	+++	++	+++	+++	++
Michael et al., 2014	+	+++	+++	++	+	+++	+
Pobric and Hamilton, 2006	+	+++	+++	++	+++	+++	++

Schuwerk et al., 2014	+	+++	+++	++	+++	+++	++
Silani et al., 2013	+	+++	+	++	+++	+++	+
Uddin et al., 2006	+	+++	+++	++	++	+++	++
Young et al., 2010	+	+++	+++	++	+++	+++	++

+ = weak, ++ = moderate, +++ = strong

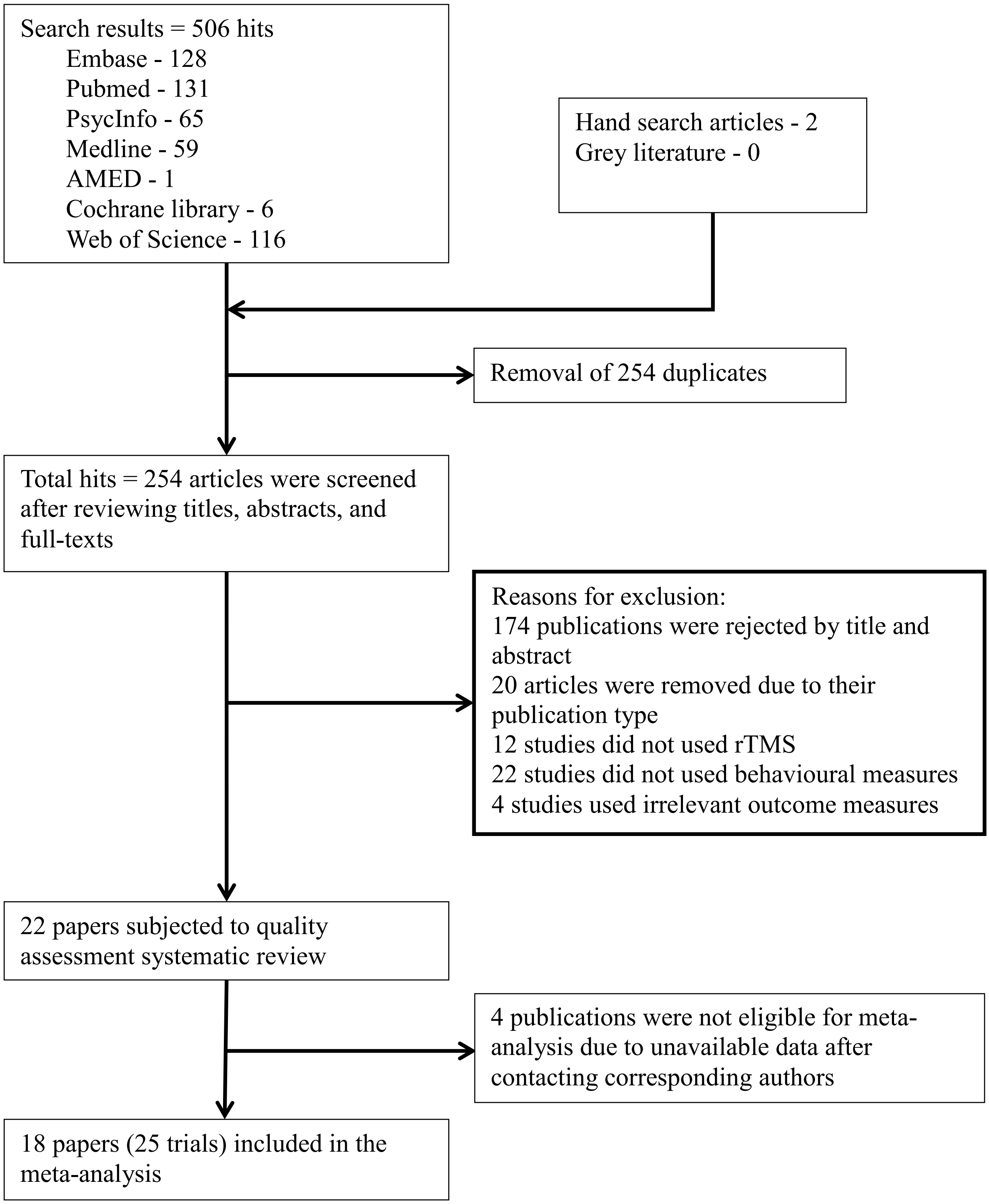

Figure S1. Study Selection and Search Results

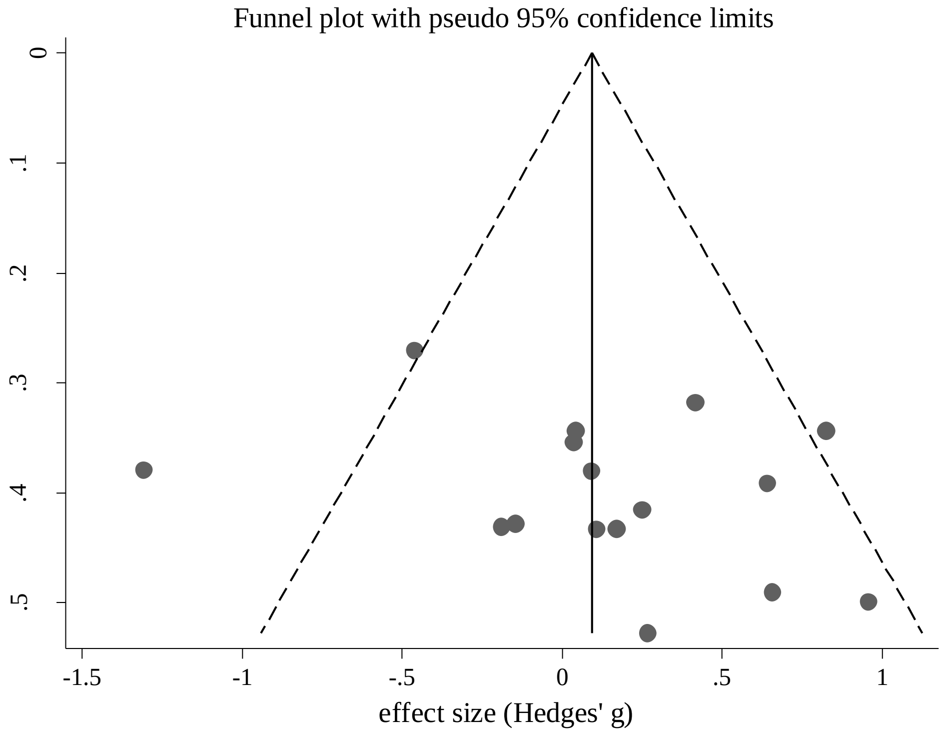

Figure S2a. Funnel plot of cognitive ToM trials included in the meta-analysis

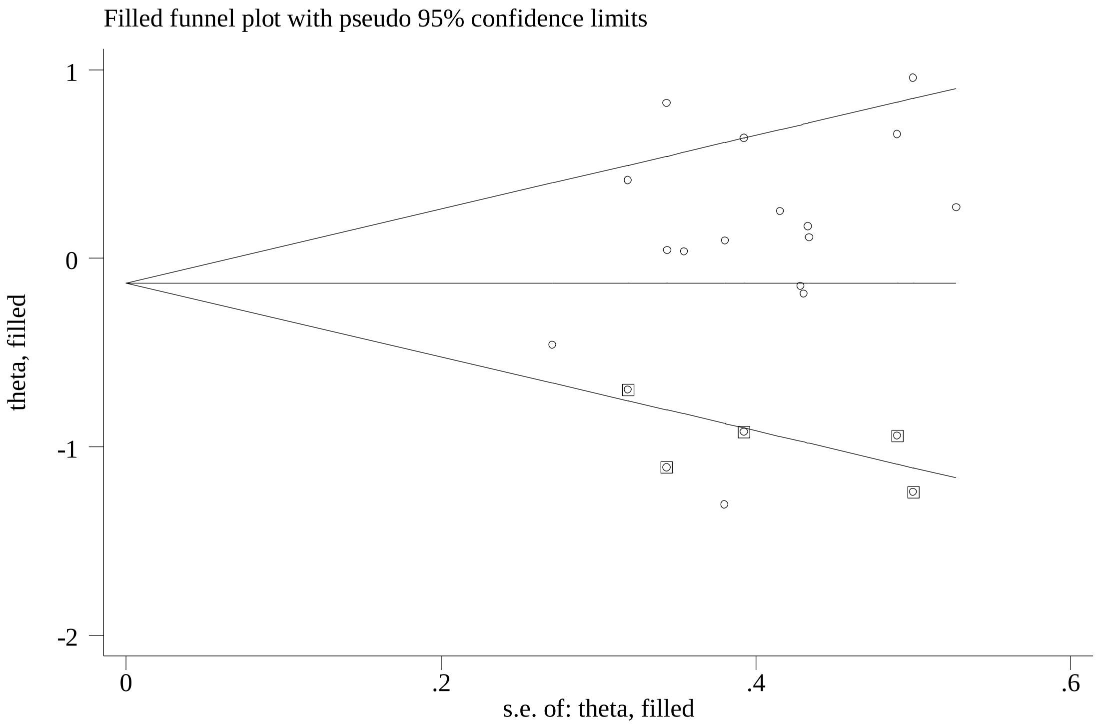

Figure S2b. Filled funnel plot of the cognitive ToM trials in the meta-analysis after trim procedure

Empty dots with an outer square represent imputed missing trials.

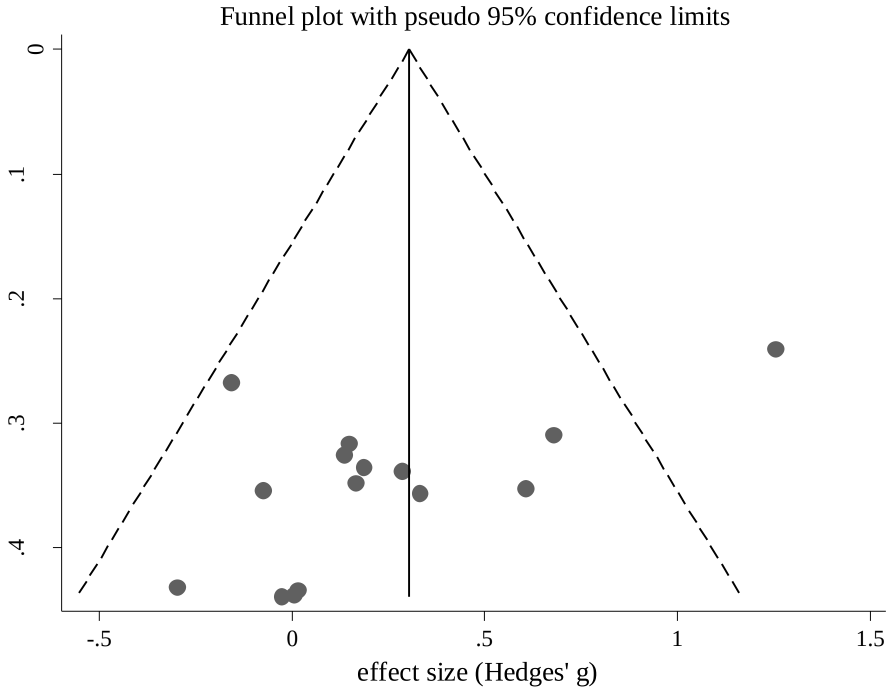

Figure S3a. Funnel plot of the affective ToM trials in the meta-analysis

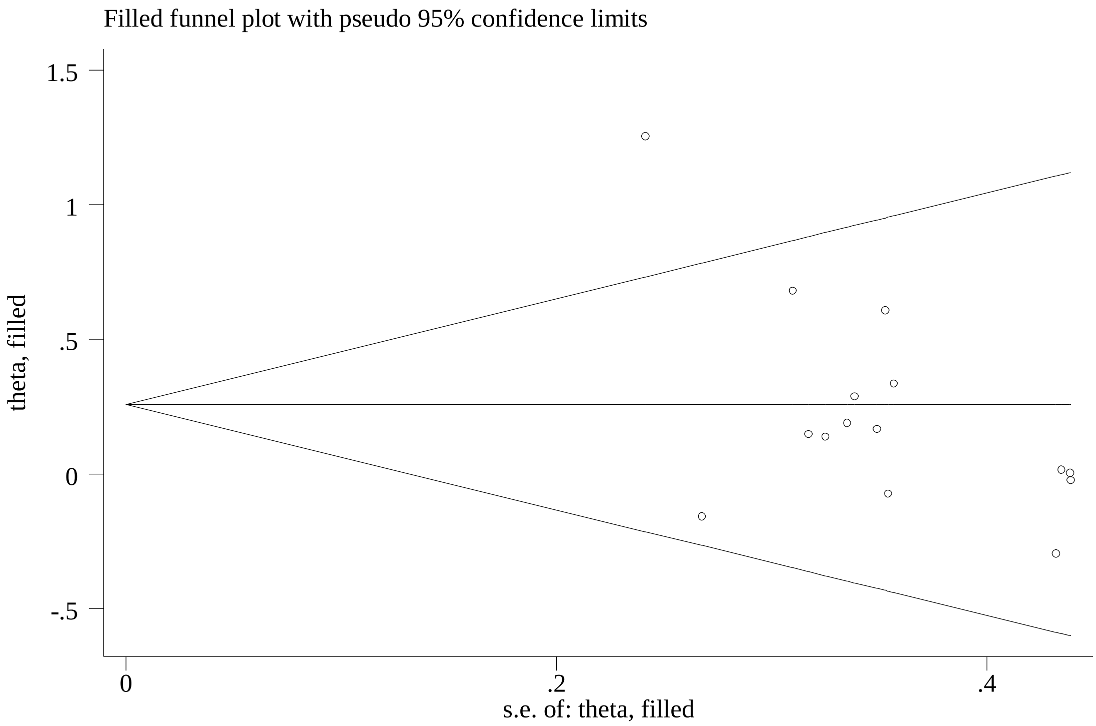

Figure S3b. Filled funnel plot of the affective ToM trials in the meta-analysis after trim procedure

No missing trials were found.