Social cognition in multiple sclerosis: a meta-analysis

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Abstract

Multiple sclerosis (MS) is associated with cognitive decline and impairment in social functioning. Accumulating evidence suggests that patients with MS are impaired in social cognition, including theory of mind (ToM) and emotion recognition. In this meta-analysis of 24 studies, facial emotion recognition and ToM performances of 989 patients with MS and 836 healthy controls were compared. MS was associated with significant impairments with medium effect sizes in ToM (d=0.57) and facial emotion recognition (d=0.61). Among individual emotions recognition of fear and anger were particularly impaired. The severity of social cognitive deficits was significantly associated with non-social cognitive impairment. These deficits in social cognition may underpin difficulties in social functioning in MS. However, there is a need for further studies investigating the longitudinal evolution of social cognitive deficits and their neural correlates in MS.

Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system characterized by multifocal destruction of myelin sheaths and axonal loss (Compston et al 2002; Geurt and Barkhof, 2008). It is usually diagnosed in young adulthood and its prognosis is variable and unpredictable. MS presents with motor, sensory and other neurological deficits, neuropsychiatric symptoms and cognitive decline (Chiaravalloti and DeLuca 2008; Compston et al 2002; Rosti-Otajärvi and Hämäläinen, 2013; Stroeber et al 2014) leading to significant functional impairment including difficulties in social functioning and employment (Krause et al 2013; Rao et al 1991b).

Cognitive deficits, a common feature of MS, are well studied and can contribute to functional impairment in this condition (Chiaravalloti and DeLuca 2008; Langdon 2011; Rao et al 1991a). Hallmark of neurocognitive impairment in MS is abnormalities in information processing, particularly processing speed (Prakash et al 2008; Van Schependom et al 2014). Other cognitive deficits in MS include impairments in learning and memory, verbal fluency and executive functioning (Prakash et al 2008). Cognitive impairment in MS is detectable from the earliest stages of MS and is generally more evident in progressive types such as secondary progressive (SP) MS (Planche et al 2015). Microstructural abnormalities and lesions in white matter significantly disrupt structural and functional connectivity between various brain regions. Inefficient activity in brain networks caused by these changes contributes to cognitive deficits in MS(Cruz-Gómez et al 2014; Schoonheim et al 2015). However, the aetiology of cognitive deficits in MS are multifactorial: other than white matter pathology, cortical atrophy, cortical lesions, and abnormalities in deep gray matter contribute to cognitive decline in MS (DeLuca et al 2015; Filippi et al 2010). While acute inflammatory relapses can affect cognitive functioning, cognitive decline in MS is usually insidiously progressive (DeLuca et al 2015). Evidence also suggests that cognitive reserve, level of premorbid intellectual development determined by variations in neurodevelopmental processes (i.e genetics, nutrition, physical health) and levels of environmental enrichment (i.e parenting, education, professional and leisure activities), is an important moderator of relationship between cognitive decline and brain pathology in MS (DeLuca et al 2015; Sumowski and Leavitt, 2013). In MS, patients with higher cognitive reserve seem to have less cognitive decline than other patients with similar severity of brain pathology.

In addition to difficulties in traditional neuropsychological tests, social cognitive impairment has been shown to be a feature of a number of psychiatric and neuropsychiatric disorders (Bora et al 2013; Bora et al 2015a). The recognition of emotions from facial cues is the most commonly studied social cognitive ability. In the human brain, a network of limbic structures that includes the amygdala, insula, orbitofrontal cortex and subcortical structures are activated in response to emotional features in faces (Fusar-Poli et al 2009; Hsieh et al 2012). Another key social cognitive ability is theory of mind (ToM), the ability to attribute mental states (feelings, beliefs, intentions, and desires) to others and understand and predict others' behaviour based on their mental states. Evidence suggests that ToM ability is associated with activation in the medial prefrontal cortex(mPFC) and posterior temporoparietal junction (pTPJ) in response to the very different type of stimuli (Schaafsma et al 2015). ToM is not an entirely homogeneous concept or ability, and ToM tasks differ in the magnitude of cognitive demand, nature of stimuli (emotional vs cognitive mental state) and mode of presentation (verbal versus visual). One important distinction between ToM tasks is whether they measure abilities to use perspective taking (ToM-PT) or decoding (ToM-decoding) based on emotional and perceptual cues to infer others' thoughts, beliefs, emotions. ToM-PT, which was also called as mental state reasoning (Sabbagh, 2004), is most typically assessed by tasks measuring false belief and indirect speech comprehension. The Reading of the mind in the eyes test (RMET) is the most commonly used task to assess ToM-decoding (Baron-Cohen et al; Sabbagh et al 2004). Evidence also suggests that there are some differences in the neural network involved in different aspects of ToM. Beyond common activations in the core network of mPFC and pTPJ, there are considerable activation differences in neighboring and other more distant brain regions depending on the task used (Schaafsma et al 2015).

Social cognitive deficits, including impairment in emotion recognition and ToM, may be clinically relevant impairments for MS patients as effective and adaptive social functioning depends critically on social cognition and MS is associated with significant psychosocial impairment including difficulties in employment and interpersonal domains (Krause et al 2013; Rao et al 1991b). Subtle difficulties in recognizing others' emotional expressions, empathic abilities, reading their complex mental states and understanding pragmatic language statements (such as irony) can contribute to interpersonal problems observed in MS. Evidence also suggests that MS patients might also subjectively report difficulties in recognizing their own emotions and empathy (Chahraoui et al 2014; Gleichgerrcht et al 2015). White and gray matter pathology in MS affects multiple brain regions and disrupts a

number of neural networks that play key roles in social cognition. However, neuropsychological studies in MS have only recently started to focus on social cognitive deficits. These studies have provided some evidence of impairment in social cognition including ToM and emotion recognition abilities in MS (Berneiser et al 2014; Cecchetto et al 2014; Pöttgen et al 2013; Roca et al 2014). However, a number of studies have failed to find such deficits, especially for emotion recognition (Di Bitonto et al 2011; Jehna et al 2010; Jehna et al 2011). Currently, the severity of social cognitive deficits in comparison to other neuropsychological difficulties is not clear, and it is not known whether recognition of some emotions or different aspects of ToM are differentially impaired in MS. The primary goal of this meta-analysis was to quantify the magnitude of social cognitive deficits, to examine if some aspects of social cognition are relatively more impaired in MS than others, and to explore the relationship between social cognitive impairment and other clinical variables in MS.

Methods

Study selection

We followed MOOSE and PRISMA guidelines in conducting this meta-analysis (Moher et al 2009; Stroup et al 2000). A literature search was conducted using the databases Pubmed, PsycINFO, ProQuest and Scopus to identify the relevant studies (January 1998 to September 2015) using the combination of keywords as follows: (Theory of mind or emotion recognition or social cognition) and multiple sclerosis. Reference lists of published reports were also reviewed for additional studies and Google Scholar was to retrieve unpublished material including conference papers and theses. Inclusion criteria were studies that: (1) Compared ToM or facial emotion recognition performances of MS and healthy controls; (2) reported sufficient data to calculate the effect size and standard error of the social cognition measure. Two brain imaging studies (Krause et al. 2009; Mike et al. 2013) and a thesis whose samples overlap with two included study (Banati et al. 2010; Berneiser et al 2014) were excluded. We contacted authors of two conference papers for unpublished data or papers but we were unable to ascertain this data. Studies investigating emotion recognition abilities with methods other than facial recognition were excluded as only a few studies investigated MS using such methods (i.e. vocal).

---------- Figure-1 Flow Diagram for meta-analysis of social cognition deficits in MS (Approximately here) ----------

Social cognition measures

Studies have investigated facial emotion recognition with a variety of methods (different sets of images of faces to label: most commonly Ekman) (Ekman and Friesen, 1976). Different ToM tasks have been utilized across studies, most commonly faux pas recognition (the task involves recognizing faux pas in series of short stories) and Reading the Mind in the Eyes Task (RMET); other tasks have included Happe stories and different versions of false belief and intention tasks (Baron-Cohen et al 2001; Stone et al 1998). In RMET, individuals are instructed to look at a series of photographs of just the eye region of the face, and picking which of four words best describe what the person in the photo is thinking or feeling. RMET was the only measure for ToM-decoding. All other ToM tasks were measuring ToM-PT.

Statistical analyses

For studies that reported more than one ToM task, pooled effect sizes and standard error values were calculated. A pooled effect size of social cognition based on ToM and/or total emotion recognition score was calculated for each study. Individual tasks analyses for two ToM measures (RMET, faux pas recognition) were also possible. A pooled effect size of ToM-PT was also calculated by averaging effect size of ToM tasks other than RMET. In addition to the total emotion labeling score, separate effect sizes for six basic emotions (anger, fear, disgust, sadness, happiness, surprise) were also calculated. An additional analysis of facial emotion recognition was conducted to calculate mean effect size of studies that used Ekman stimuli.

Meta-analyses were performed using packages in the R environment (OpenMetaAnalyst, Metafor) and MIX software version 1.7 on a Windows platform (Bax et al 2006; Viechtbauer , 2010; Wallace et al 2012). Effect sizes were weighted using the inverse variance method. Several studies included subgroups of MS and shared control groups (Brandon, 2015; Dulau, 2014; Ouellet et al 2010; Radlak, 2014) (See Table 1). Therefore, we divided n of control groups between comparisons not to overestimate the contribution of these studies to overall effect size. A random effects model (DerSimonian–Laird estimate) was used. Homogeneity of the distribution of weighted effect sizes was tested with the Q and I^2 tests. Tau-squared (τ^2), an estimate of between-study variance, was used as a measure of heterogeneity in the random effects model. Publication bias was assessed by inspection of funnel plots, Egger's test and trim and fill method. Egger's test relies on the theory that small studies with significant rather than negative findings in studies with small sample sizes would be more likely to be reported while large-scale studies would be more likely to be published regardless

of the significance of the findings. The significance threshold of Egger's test was defined as p=0.1 due to small numbers of studies included in some analyses.

Subgroup analyses were conducted for age (matched vs non-matched), gender (matched vs non-matched), duration of education (matched vs non-matched), depressive symptoms (No difference vs significantly increased in MS), MS severity based on EDSS (Expanded Disability Status Scale) (Mild/moderate only (EDSS cut off score 4.5 or 5) vs also includes patients with more severe symptoms), and neurocognition (impaired vs non-impaired). Cognitive impairment was defined as having a severe impairment (Cohen's d>0.8) in comparison to healthy controls in at least one measure or having a medium-sized impairment (Cohen's d>0.5) of pooled effect size of all cognitive tests used (Table-1). Q_{bet} test was used to statistically compare subgroups in these analyses. Meta-regression analyses were conducted for gender (ratio of females in MS group) with a random effects model were using the restricted-information maximum likelihood method with a significance level set at p<0.05. Other than the main meta-analysis, separate meta-analyses for social cognition (k=11), ToM (k=7) and facial emotion recognition (k=7) were conducted in studies that included only RR type MS. We also repeated the main meta-analysis of social cognition after removing 4 theses/conferences papers included. Also, a preliminary comparison of RR and chronic progressive types of MS were conducted for social cognition (k=5).

---------- Figure-2 Forest plot for facial emotion recognition differences between MS and healthy controls: Diamond shape= average effect size and its confidence interval based on random effects model; SE=Standard error of Cohen's d

-------(Approximately here) ----------

Results

Twenty-four studies (29 MS-healthy controls comparisons) involving 989 (69.3 % females) MS patients and 836 (62.1 % females) healthy controls were included (Table 1) (see Figure 1 for the flow chart of the study selection process). There was a significant but very modest difference for age; individuals with MS tended to be older than healthy controls (*d*=0.16, CI=0.0-0.31, p=0.05, k=29). In 11 samples, all MS patients were relapsing-remitting (RR) type and other 7 studies, MS patients were predominantly RR type. Two study sample included only secondary progressive (SP) MS, one sample included chronic progressive subtypes (mostly SP) of MS and another sample included only primary progressive (PP) type MS. Other studies had mixed samples. Only one of the studies included patients with

clinically isolated syndrome (CIS) and none of the studies included patients with radiologically isolated syndrome (RIS). In four studies, social cognitive abilities of RR and chronic progressive (SP and/or PP) types of MS were compared.

Social cognition was significantly impaired (*d*=0.56, CI=0.42-0.69, k=29) in MS in comparison to healthy controls (Table-2 and Supplement 1). The severity of impairment in social cognition was similar when 4 non-peer reviewed (theses and a conference paper) studies were excluded (d=0.60, CI=0.43-0.77, Z=7.0, p<0.001, τ^2=0, k=21). In separate analyses of the two key social cognitive domains investigated, the performance of MS patients was significantly poorer than healthy controls for both emotion recognition (*d*=0.61, CI=0.39-0.83, k=17, Figure-2) and ToM (*d*=0.57,CI=0.42-0.73, k=19, Figure-3) (Table-2). Distribution of effect sizes for ToM was homogeneous (p for Q=0.09, I^2= 32 %, τ^2=0.04) but there was a significant but moderate heterogeneity for facial emotion recognition (p for Q<0.001, I^2= 64 %, τ^2=0.14) (Table-2). In the subgroup analysis of studies using Ekman pictures as facial emotion stimuli, MS patients underperformed healthy controls and distribution of effect sizes were homogeneous (d=0.74, CI=0.54-0.94, Z=7.4, p<0.001, τ^2=0.01).

In the analysis of individual emotions, MS patients significantly underperformed controls in all emotions (Table 2 and Supplement 1). The severity of deficits was relatively pronounced for recognition of fear (*d*=0.54, CI=0.34-0.73, k=9) and anger (*d*=0.56, CI=0.32-0.80, k=10) (Supplement 1). Effect sizes for sadness (*d*=0.32, CI=0.16-0.49, k=9), disgust (*d*=0.25, CI=0.01-0.50, k=9), surprise (*d*=0.32, CI=0.12-0.52, k=8) and happy (*d*=0.22, CI=0.04-0.39, k=9) face stimuli indicated significant but small sized deficits (Table-2). It was possible to conduct individual analyses for two ToM tasks. There was significant impairment in RMET (*d*=0.67, CI=0.47-0.88, k=10) and ToM-PT (*d*=0.39, CI=0.17-0.61, k=14); however, while MS patients tended to underperform healthy controls in faux pas recognition between-group difference was not significant (*d*=0.25, CI=-0.04-0.55, k=9, p=0.08) (Table-2 and Supplement 1). Distribution of effects sizes for RMET and four of the six basic emotions were homogenous, but there was significant but modest heterogeneity for faux pas recognition (I^2= 55%, τ^2=0.11) , recognition of anger (p for Q=0.03, I^2= 51%, τ^2=0.07) and disgust (I^2= 48 %, τ^2=0.06) (Table-2). Egger's tests, trim and fill method (Table-2) and inspection of funnel plots (See Supplement 2) did not provide evidence of publication bias for any of the measures.

---------- Figure-3 Forest plot for ToM differences between MS and healthy controls (Approximately here) ----------

MS subtypes and social cognition

In studies that included only RR MS, social cognition was significantly impaired (*d*=0.53, CI=0.34-0.71, Z=5.5, p<0.001, τ^2=0.02, k=10). In separate analysis of social cognitive domains, RR-MS patients were significantly impaired both in ToM (d=0.48, CI=0.29-0.66, Z=5.0, p<0.001, τ^2=0, k=7) and facial emotion recognition (d=0.59, CI=0.29-0.90, Z=3.6, p<0.001, τ^2=0.12, k=8). In a preliminary analysis for the comparison of chronic progressive and RR-MS (k=5), social cognition was tended to be more impaired in chronic progressive MS in comparison to RR MS (d=0.42, CI=-0.06-0.91, Z=1.7, p=0.08, Q=1.2, p for Q=0.02, I^2= 67 %, τ^2=0.20) (Supplement 1).

Effect of confounding variables

In subgroup analyses, the severity of social cognitive impairment in patients that were matched for age to control group was similar to patients who were not matched to control group (Table-3). Same was also true for the duration of education. Impairment in social cognition in MS patients who were more depressed than controls group was not statistically different from impairment in MS patients that were matched to control group for depressive symptoms. There was no significant difference in severity of social cognitive impairment between MS samples that only included patients with mild or moderate severity and samples that included MS patients with more severe disability. MS patients who had severe non-social cognitive impairment had a more severe social cognitive deficit in comparison to other patients (Table-3). Meta-regression analysis did not find significant relationship between ratio of females in MS group and deficits in social cognition (*Z*=0.14, *p*=0.89).

Discussion

The current meta-analysis investigated social cognitive deficits in MS in comparison with healthy controls. Our findings showed that MS patients significantly underperformed healthy controls in ToM and facial emotion recognition tasks. Non-social cognitive impairment was significantly associated with social cognitive deficits.

In the current meta-analysis, medium effect sizes were found for ToM (*d*=0.57) and facial emotion recognition (*d*=0.61) deficits in MS. Severity of these deficits were much less pronounced than impairments reported for number of neurodegenerative conditions predominantly characterized by severe cortical and subcortical gray matter atrophy such as

FTD and Huntington's disease (Bora et al 2015a; Bora et al 2016), however, these findings still suggest that many patients with MS have significant difficulties in emotion recognition and ToM. Current findings suggest that social cognitive impairment, such as the poor reading of others' intentions and a key difficulty in recognition of anger and fear can potentially contribute to psychosocial and interpersonal difficulties observed in MS.

The severity of impairment in social cognition was comparable in magnitude to most non-social cognitive deficits as reported in previous meta-analyses in MS, which have reported small to medium effect sizes for most cognitive variables (Henry and Beatty 2006; Prakash et al 2008). Effects sizes for impairments in ToM and facial emotion recognition were very similar to the severity of most deficits in non-social cognitive tasks including general cognition, executive functions relatively larger (g=0.54-0.59) (Prakash et al 2008). Both decoding and reasoning aspects of ToM were impaired in MS. RMET was more sensitive than faux pas recognition in detecting mentalizing problems in MS. Emotion recognition deficits were relatively specific to fear and anger. Effect sizes of deficits in other four emotions indicated mild impairment. Also, unlike other neurodegenerative conditions, deficits in recognition anger and fear were not accompanied by severe difficulties in recognition of disgust (Bora et al 2015a; Bora et al 2016). Relative specificity of deficits in recognition of some negative emotions (anger and fear) is interesting as MS is characterized by widespread rather than focal brain abnormality. Interestingly, a similar pattern of relatively specific impairment in recognition of fear and anger has been a consistent finding in pediatric ADHD studies (Bora and Pantelis, 2015). While MS and ADHD (and associated social cognitive deficits) have very different etiologies (demyelinating/neurodegenerative *vs.* maturational) and outcomes (deterioration vs. improvement by time), both conditions share some characteristics such as information processing deficits and negative effects on the efficiency of intrinsic brain networks (Sripada et al 2014). These findings speculatively suggest the possibility that pattern of social cognitive deficits might be different in maturational or neurodegenerative conditions mainly affecting white matter integrity or functional connectivity in comparison to neurodegenerative diseases predominantly associated with loss of gray matter integrity in frontotemporal and subcortical regions. However, further work is necessary to distinguish different patterns of social cognitive deficits associated with different neuropsychiatric disorders. Also, the relatively mild deficit in recognition of happiness is not specific to MS and is common finding across different neuropsychiatric disorders. Task difficulty might play a role in the relatively good performance of recognition of happy emotions and poor performance in some negative

emotions across disorders (Rosenberg et al 2014). Positive emotions other than recognition of happiness have been rarely used in neuropsychological research in neurological disorders. Studies using more complex positive emotional stimuli can potentially reveal more severe recognition deficits in MS.

Social cognitive deficits observed in this meta-analysis were not significantly related to depressive symptoms or physical disability, as measured by EDSS, in MS samples. These findings suggest that social cognitive impairment observed in MS is not simply caused by low mood and physical disability. However, it is important to note that most individuals with MS in included studies did not meet criteria for clinical depression, it might be expected that social cognitive, especially ToM, deficits could be exacerbated during depression – as is seen in subjects without neurological disorders (Bora and Berk, 2016). It is also not known if impairments in insight and neuropsychiatric symptoms such as apathy, euphoria, aggression – which are observed in some patients with MS – are related to social cognitive deficits, as these have not been extensively explored in this disorder. The lack of association between physical disability (as measured by EDSS) and social cognition is not surprising as EDSS has only one item which assesses cognition (subjectively) and higher scores mainly reflect problems in mobility. For example, patients with lesions mainly affecting the spinal cord and pyramidal tracts could have very high scores in EDSS without much evidence of cognitive deficits. Future studies including other measures of physical disability, such as Multiple Sclerosis Functional Composite (MSFC), might show better correlations between the level of physical disability and impairments in social functioning and social cognition (Hanken et al 2015). We were not able to investigate the effect fatigue, another important potential moderator on social cognitive performance in MS, due to lack of social cognition studies reporting this variable. Previous studies have shown that MS-related fatigue is associated with poor performance in tasks assessing vigilance (Bora et al 2015b) and effects of fatigue on social cognition should be investigated further. Another consideration is the effect of subtypes of MS on social cognitive deficits. Our findings in RR type of MS suggested that social cognitive deficits are evident in non-progressive MS. Only four studies have compared performances of RR and chronic progressive types of MS. While three of these studies reported more severe deficits in SP compared to RR type (Berneiser et al 2014; Brandon, 2015; Radlak, 2014), between-group differences were not significant in the fourth study (Dulau, 2014). A preliminary meta-analysis of these four studies suggested that social

cognition is tended to be more impaired in chronic progressive than RR MS. In MS studies, among potential proxy measures of cognitive reserve (premorbid IQ, employment, parental measures and education), duration of education is the most commonly used measure. In previous neurocognitive and brain imaging studies in MS, duration of education was shown to be a significant moderator. In the current meta-analysis, differences for duration education (patients vs. controls) was not associated with social cognitive differences between MS and healthy controls. This finding suggests that duration of education is the not the best proxy measure for premorbid social cognitive abilities. Measures assessing premorbid social functioning can be expected to reflect premorbid social cognition better and should be considered to be included in future studies investigating social cognition in MS.

Neurocognitive impairment in MS was significantly associated with more severe social cognitive deficits. These findings are in line with previous findings in other neuropsychiatric disorders including Huntington's disease and frontotemporal dementia (Bora et al 2015a; Bora et al 2015c). Non-social cognitive impairment including attention, executive dysfunction and perceptual abnormalities (i.e. face recognition) can contribute to social cognitive impairment in MS. Impairment in social cognition in MS is likely to be multi-factorial, with non-specific (cognitive impairment, fatigue) and specific (i.e. abnormalities in brain regions involved in social cognition) factors playing a role. Few studies have directly investigated the relationship between brain imaging abnormalities and social cognition in MS. Mike et al (2013) reported that disconnection between cortical regions involving the processing of emotions and socially relevant information can be related to deficits in facial emotion recognition in MS. This study also reported an association between cortical atrophy (temporal and prefrontal cortices) and performance in RMET but not in faux pas recognition. In another study, Krause et al (2009) found that poor performance in recognition of unpleasant emotions (anger, fear and sadness) was related to less activation in the insula and ventrolateral prefrontal cortex. However, in MS patients who differ from controls in behavioral performance, Passamonti et al (2009) reported increased ventrolateral prefrontal cortex activation but also decreased functional connectivity between frontal cortex and the amygdala. In a fourth study, Jehna et al (2011) found increased activation in the posterior cingulate cortex and precuneus for anger and disgust in MS patients who have not behaviorally performed poorer than healthy controls. There is a need for further investigation into the neural correlates that underpin these deficits, to elucidate the neurobiological mechanisms of ToM and emotion recognition deficits in MS.

Effects of currently available disease-modifying treatments of MS on delaying social cognitive deficits are not known. However, there is some evidence suggesting positive effects of these treatments on cognitive deficits (Lyros et al 2010) and same can be expected for social cognition. Early psychopharmacological interventions may have the potential to delay social cognitive deficits and the resultant disability in social and vocational functioning. Some evidence also suggests that cognitive rehabilitation can – at least partially – remediate cognitive deficits in MS (Mitolo et al 2015) and future studies may consider incorporating social cognition in training programs to improve social functioning in MS.

There are a number of limitations to our meta-analysis. We were not able to investigate emotion recognition deficits beyond facial stimuli. However, preliminary evidence suggests that MS is also associated with deficits in recognition of non-facial stimuli including vocal prosody and body language (Beatty et al 2003; Cecchetto et al 2014; Kraemer et al 2013). The heterogeneity of social and cognition measures was another limitation. To overcome this limitation, we conducted individual task analysis when possible. Another consideration is psychometric limitations of social cognition tasks in comparison to traditional neuropsychological batteries (Johnston et al 2008). There is a need for further development of standardized batteries for assessment of social cognition in neuropsychiatric disorders. Heterogeneity of the samples such as differences in duration of illness, demographic characteristics, depressive symptoms across studies and inclusion of varying proportions of individuals with different subtypes of MS. Therefore, we conducted a number of subgroup analyses. Also, available studies have focused on RR and chronic progressive subtypes of MS. There is a need for studies investigating social cognition in RIS and CIS. Another limitation was that a relatively smaller number of studies was included in the meta-analysis of individual emotions.

In conclusion, our findings suggest that MS is associated with significant deficits in social cognition. The severity of these impairments is relatively modest (medium effect sizes) but comparable to other cognitive deficits in MS. Social cognitive impairment is likely to contribute to poorer social functioning in many individuals with MS. Future studies investigating the course of social cognitive deficits, and studies further exploring the neural correlates of these impairments in MS are necessary.

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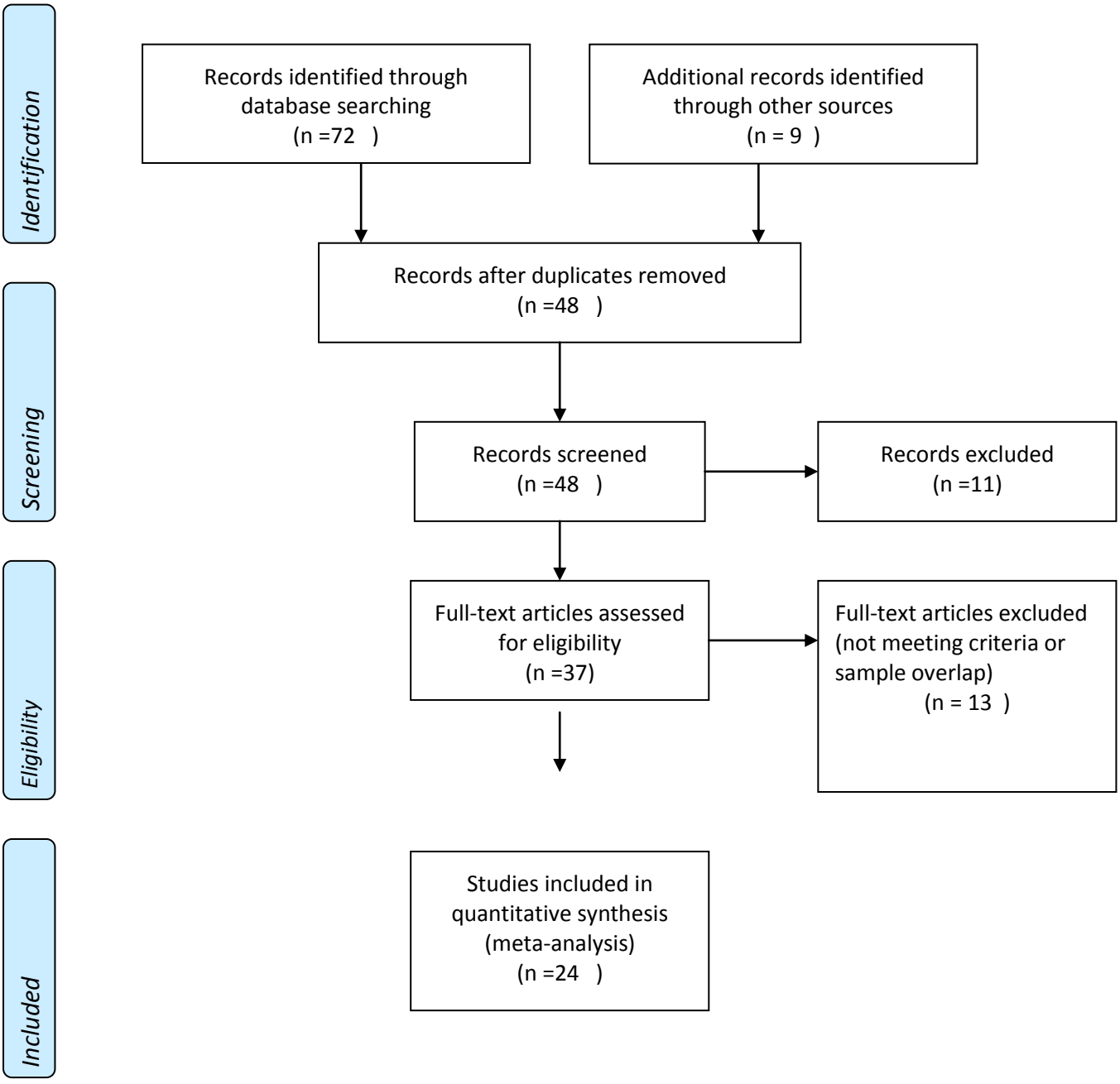
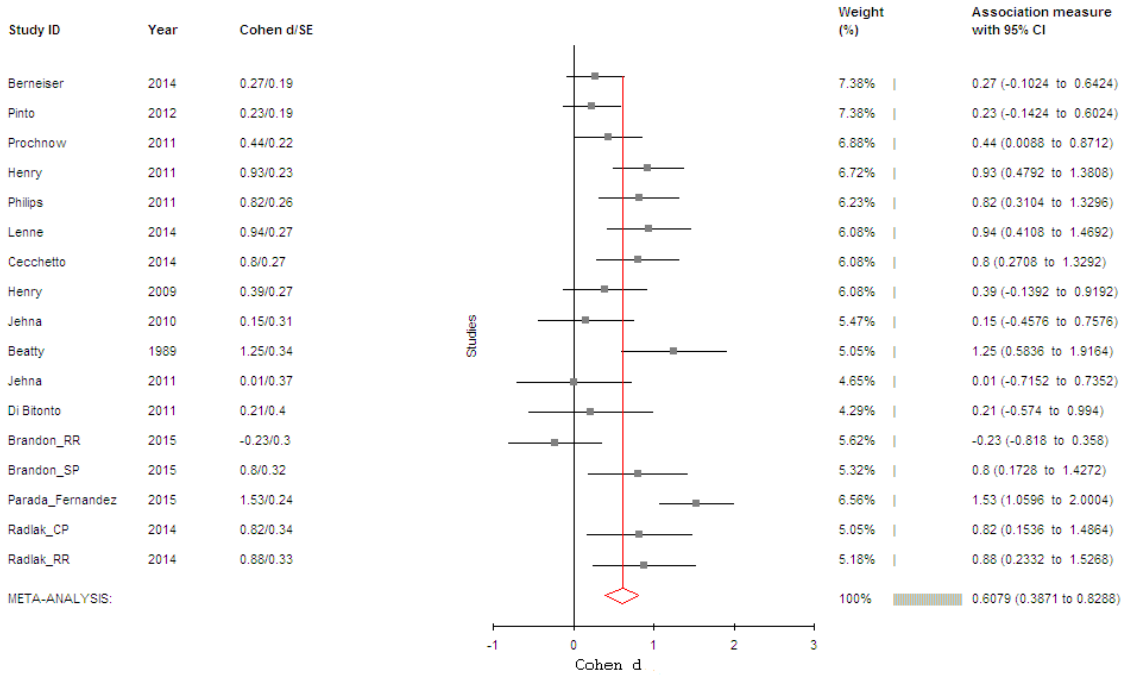
Figure 1-Flow Diagram for meta-analysis of social cognition deficits in MS




Study ID
Year
Cohen d/SE
Weight (%)
Association measure with 95% CI
Berneiser 2014 0.27/0.19 7.38% 0.27 (-0.1024 to 0.6424)
Pinto 2012 0.23/0.19 7.38% 0.23 (-0.1424 to 0.6024)
Prochnow 2011 0.44/0.22 6.88% 0.44 (0.0088 to 0.8712)
Henry 2011 0.93/0.23 6.72% 0.93 (0.4792 to 1.3808)
Philips 2011 0.82/0.26 6.23% 0.82 (0.3104 to 1.3296)
Lenne 2014 0.94/0.27 6.08% 0.94 (0.4108 to 1.4692)
Cecchetto 2014 0.8/0.27 6.08% 0.8 (0.2708 to 1.3292)
Henry 2009 0.39/0.27 6.08% 0.39 (-0.1392 to 0.9192)
Jehna 2010 0.15/0.31 5.47% 0.15 (-0.4576 to 0.7576)
Beatty 1989 1.25/0.34 5.05% 1.25 (0.5836 to 1.9164)
Jehna 2011 0.01/0.37 4.65% 0.01 (-0.7152 to 0.7352)
Di Bitonto 2011 0.21/0.4 4.29% 0.21 (-0.574 to 0.994)
Brandon_RR 2015 -0.23/0.3 5.62% -0.23 (-0.818 to 0.358)
Brandon_SP 2015 0.8/0.32 5.32% 0.8 (0.1728 to 1.4272)
Parada_Fernandez 2015 1.53/0.24 6.56% 1.53 (1.0596 to 2.0004)
Radlak_CP 2014 0.82/0.34 5.05% 0.82 (0.1536 to 1.4864)
Radlak_RR 2014 0.88/0.33 5.18% 0.88 (0.2332 to 1.5268)
META-ANALYSIS: 100% 0.6079 (0.3871 to 0.8288)
Studies
-1
0
1
2
3
Cohen d

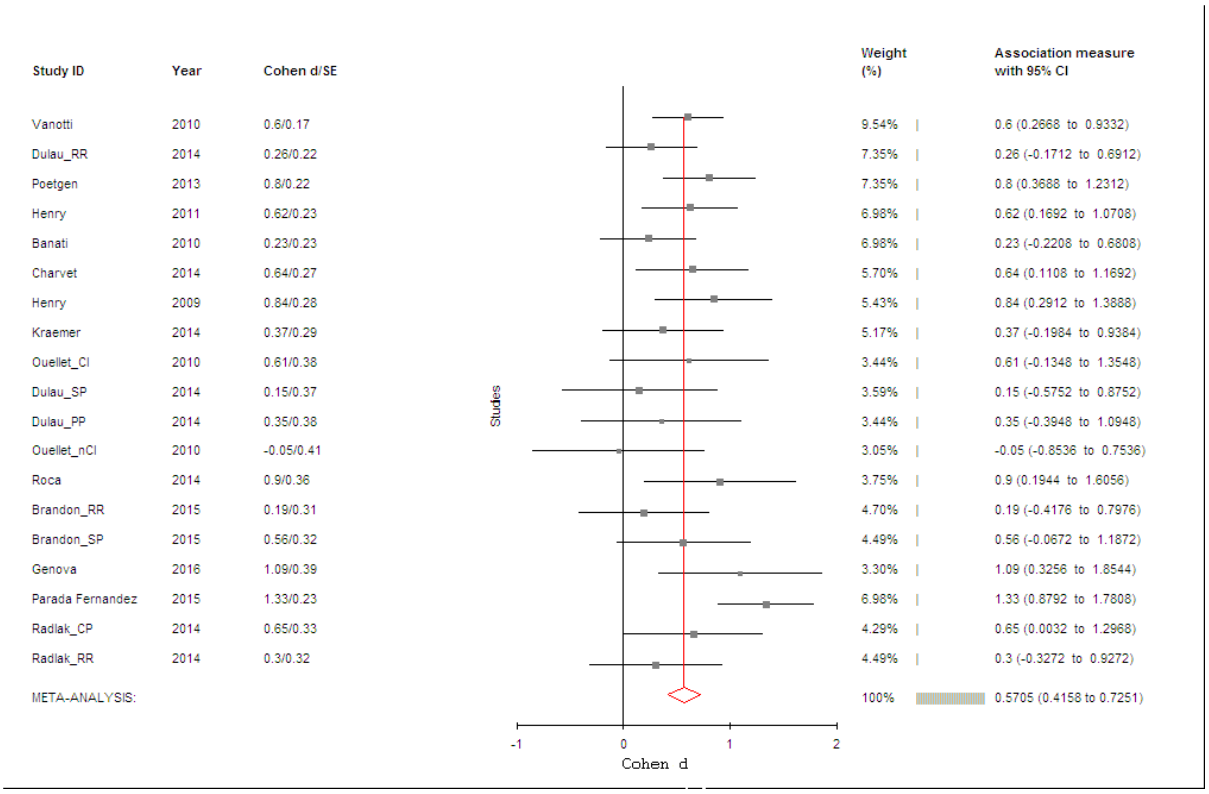

Study ID
Year
Cohen d/SE
Weight (%)
Association measure with 95% CI
Vanotti 2010 0.6/0.17 9.54% 0.6 (0.2668 to 0.9332)
Dulau_RR 2014 0.26/0.22 7.35% 0.26 (-0.1712 to 0.6912)
Poetgen 2013 0.8/0.22 7.35% 0.8 (0.3688 to 1.2312)
Henry 2011 0.62/0.23 6.98% 0.62 (0.1692 to 1.0708)
Banati 2010 0.23/0.23 6.98% 0.23 (-0.2208 to 0.6808)
Charvet 2014 0.64/0.27 5.70% 0.64 (0.1108 to 1.1692)
Henry 2009 0.84/0.28 5.43% 0.84 (0.2912 to 1.3888)
Kraemer 2014 0.37/0.29 5.17% 0.37 (-0.1984 to 0.9384)
Ouellet_CI 2010 0.61/0.38 3.44% 0.61 (-0.1348 to 1.3548)
Dulau_SP 2014 0.15/0.37 3.59% 0.15 (-0.5752 to 0.8752)
Dulau_PP 2014 0.35/0.38 3.44% 0.35 (-0.3948 to 1.0948)
Ouellet_nCI 2010 -0.05/0.41 3.05% -0.05 (-0.8536 to 0.7536)
Roca 2014 0.9/0.36 3.75% 0.9 (0.1944 to 1.6056)
Brandon_RR 2015 0.19/0.31 4.70% 0.19 (-0.4176 to 0.7976)
Brandon_SP 2015 0.56/0.32 4.49% 0.56 (-0.0672 to 1.1872)
Genova 2016 1.09/0.39 3.30% 1.09 (0.3256 to 1.8544)
Parada Fernandez 2015 1.33/0.23 6.98% 1.33 (0.8792 to 1.7808)
Radlak_CP 2014 0.65/0.33 4.29% 0.65 (0.0032 to 1.2968)
Radlak_RR 2014 0.3/0.32 4.49% 0.3 (-0.3272 to 0.9272)
META-ANALYSIS: 100% 0.5705 (0.4158 to 0.7251)
Studies
-1
0
1
2
Cohen d

Table-1 Clinical and demographic characteristics of the studies included in the meta-analysis

First author	Sample	Cognitive tasks	Social cognition task	Characteristics	MS symptoms	Medication	Outcome
Banati et al 2010	40 MS 35 HC	IQ	Faux pas RMET	Age=36.2	37 RR, 3 SP EDSS=2.3 All EDSS<4.5	No mention	Nonverbal ToM impaired Faux pas impaired only in patients with more severe disability
Beatty et al 1989	21 MS 19 HC	BFRT MMSE	Face emotion (Ekman)	Age=52 Duration=18.4 EDSS=6.6	Chronic progressive EDSS=6.6 BDI=7.3		Impaired
Bernesier et al 2014	61 MS 53 HC	PASAT (only MS)	Face emotion (FAB)	Age=42.2 Duration=6.1 BDI=9.2	RR=47, SP=11 PP=3 EDSS=3.7	No details	MS impaired More in SP than RR
Brandon 2015	31 HC	PASAT, SDMT, Verbal memory, Verbal fluency, TMT, Stroop, Digit span, BFRT	Face emotion (ACS) RMET			No details	
-RR*	34 MS			Age=46.1 Duration=7.4	All RR		No difference
-SP*	32 MS			Age=56.9 Duration=20.2	All SP		MS impaired
Cecchetto et al 2014	30 MS 30 HC	IQ PASAT, SDMT, other tasks (only patients)	Face emotion (Nim Set)		All RR EDSS<4.5 Mean=2	No details	MS impaired
Charvet et al 2014	28 MS 32 HC	IQ, SDMT	RMET Faux pas False belief	Age=16.3 Duration=2.5(2.5)	Pediatric onset EDSS<4.5 Median EDSS=1	No details Steroid free for 30 days or more	Impaired Correlated with SDMT
Di Bitonto et al 2011	13 MS 13 HC	BFRT	Face emotion (Ekman)	Age=42	All RR EDSS=2.8(1.6)	All on immune modulatory treatment	No difference
Dulau 2014		WCST, letter fluency, Stroop, PASAT	RMET Faux pas Intention			No details	Social cognitive impairment Pronounced in cognitively impaired

							patients
-RR	30 MS 80 HC			Age=41 Duration=11.5	EDSS=2 (0-4.5)		RMET impaired
-SP*	15 MS 29 HC			Age=51 Duration=18.8	EDSS=4		No significant difference from RR
-PP*	15 MS 29 HC			Age=54.8 Duration=10	EDSS=4		No significant difference from RR
Genova et al 2016	15 MS 15 HC	SDMT, PASAT, Digit span, verbal learning	TASIT ToM	Age=49.5 Duration=18	10 RR, 5 chronic progressive	No details	Impaired
Henry et al 2009	27 MS 30 HC	Semantic & letter Fluency, SDMT Vocabulary Verbal learning	Face emotion (Ekman) RMET	Age=47 Duration =7(6)	Disease steps=1.9(2.0)	No details	ToM, anger, fear impaired Correlated with fluency
Henry et al 2011	64 MS 30 HC	IQ Brixton	False belief Faux pas Face emotion (Ekman)	Age=42.4 Duration=9.1	ALL RR EDSS<5.5 EDSS=2.3	No details	Impaired in social cognition
Jehna et al 2010	20 MS 23 HC		Facial emotion	Age=36.4 Duration=7.3	12 Clinicaly isolated 7 RR, 1 SP EDSS=1.7(0.9)	No details	No difference in accuracy Reaction to emotional stimuli slower in MS
Jehna et al 2011	15 MS 15 HC	PASAT, WCST, SDMT, verbal fluency, memory	Face emotion (BERT)	Age=29.5 Duration=3.3	All RR EDSS=1.7 EDSS<4	14/16 immune modulatory treatment	No impairment in emotion recognition
Kraemer et al 2014	25 MS 25 HC	Stroop, TMT, Number-letter	MASC	Age=30.9 Duration=1.2 All<2 years	All RR EDSS=0.96 EDSS<2.5	22/25 on immune modulatory treatment BDI=9.2	ToM impaired ToM correlated with Stroop
Lenne et al 2014	55 MS 21 HC	PASAT, Digit span, Verbal learning, Digit symbol, Verbal Fluency, Go NoGo	Face emotion (Ekman)	Age=39.8 Duration=7.5(6)	All RR EDSS=2(median)	Not mentioned	Impaired Especially anger, sadness and fear

Ouellet 2010 (43)	41 MS 20 HC	26 Cognitively impaired 15 not-impaired	Faux pas Happe stories C I		22 RR, 13SP, 5 SP	Not mentioned	ToM impaired More in cognitively impaired group
Parada-Fernandez 2015	45 MS 40 HC		Face emotion (FEEL) RMET	Age=49.4	24 RR, 21 chronic progressive	No detail	Impaired
Philips et al 2011	32 MS 33 HC	BFRT Verbal fluency, Go NoGo, Verbal memory	Face emotion (Ekman Morphed)	Age=44.0 Duration=7.9(5.5)	27 RR, 2 SP, 3 PP Disease steps= 2.2(1.7)	21/27 RR on disease modifying treatment (mostly on interferon)	Impaired
Pinto et al 2012	56 MS 56 HC	BFRT matched MS only: Digit span, WCST, Verbal learning, fluency	Face emotion (Nim Set)	Age=38.9 Duration=9(6.2)	48 RR, 3 SP, 5 PP EDDS=2.5(2.0) HDRS=4.5	Not mentioned	No difference Correlated with neurocognition
Pottgen et al 2013	45 MS 45 HC	MS only: SDMT, verbal memory, Nonverbal logical reasoning	MASC	Age=42.4 Duration=8.5(6.1)	31 RR, 8 SP, 6 PP EDSS=3.5	Not mentioned	MS impaired in ToM Remains to be impaired After exclusion of subjects With severe cognitive deficit, clinical depression or high EDSS (>3.5)
Prochnow et al 2011	35 MS 61 HC	All BFRT and neutral emotion recognition normal	Face emotion (Ekman and PCFAE)	Age=48.1 Duration=9.2(8.4)	EDSS-median 6 BDI=11.4 29 SP, 5 RR, 1 PP	All-immunosuppresants Mitoxantrone 80 %	Impaired in fear, anger, Surprise, sad faces Disgust impaired in patients with higher EDSS
Radlak 2014	31 HC	Verbal fluency, SDMT	Face emotion (Ekman) TASIT ToM				
-CP*	26 MS			Age=55.7 Duration=14.1	23 SP, 3 PP PDDS=5.4 (1.7) 0-8 HDRS=7	None on disease modifying treatment	Impaired in ToM and emotion recognition

-RR*	30 MS			Age=44.7 Duration=10.1	PDSS=1.8 (1.7) 0-5 HDRS=4.2	16/31 on disease modifying treatment	Impaired in emotion recognition
Roca et al 2014	18 MS 16 HC	PASAT, FAB, Digit Span, WCST, TMT, Verbal fluency	Faux pas	Age=40.7 Duration=5.1 (3.8)	All RR Mild (EDSS 0-3) Mean=0.6	All on disease modifying treatment	Impaired in cognitive score only Correlated with neurocognition
Vanotti et al 2012	121 MS 53 HC	PASAT	RMET	Age=36.4 Duration=3.5(0.3)	All RR EDSS=2.5(1.5)		Impaired Correlated with PASAT and fatigue

MS=Multiple sclerosis, RR=Relapsing-remitting, PP=Primary progressive, SP= Secondary progressive, EDSS= Expanded Disability Status Scale,
BDI= Beck Depression inventory, PASAT= Paced Auditory Serial Addition Test SDMT= Symbol Digit Modalities Test, RMET=Reading the mind from the eyes test, BFRT=Benton facial recognition test,
FAB=Frontal assessment battery, WCST=Wisconsin cart sorting test, TMT=Trail making test
MASC= Movie for the Assessment of Social Cognition, FAB=Florida Affect Battery, ACS=Advanced Clinical Solutions social perception subtest,
BERT=Behavioral Emotion Recognition Test, PCFAE= Test of Perceptual Competence of Facial Affect Recognition
PDDS=Patient determined disease steps, *=Sharing control group

Table-2 mean weighted effect sizes for differences between patients with MS and healthy controls on social cognition tasks

Test	Study N	MS	HC	d	95 % CI	Z	P	Q	Q (p)	τ^2	Bias (p)	I^2 (%)	Estimated Cohen d(CI) Trim and fill
Social cognition	29	989	836	0.56	0.42-0.69	8.2	<0.001	48.4	0.001	0.05	0.93	42	No change
ToM	19	651	512	0.57	0.42-0.73	7.2	<0.001	26.5	0.09	0.04	0.48	32	No change
-ToM-PT	14	392	358	0.39	0.17-0.61	3.5	<0.001	25.7	0.02	0.08	0.21	49	No change
-Faux pas	9	251	242	0.25	-0.04-0.55	1.7	0.09	17.9	0.02	0.11	0.35	55	No change
-RMET	10	387	330	0.67	0.47-0.88	6.4	<0.001	14.1	0.12	0.04	0.28	36	No change
Facial emotion	17	596	486	0.61	0.39-0.83	5.4	<0.001	46.3	<0.001	0.14	0.75	65	No change
-Anger	10	366	297	0.56	0.32-0.80	4.6	<0.001	18.5	0.03	0.07	0.84	51	No change
-Fear	9	310	241	0.54	0.34-0.73	5.6	<0.001	9.0	0.35	0.01	0.10	11	No change
-Sad	9	351	282	0.32	0.16-0.49	3.8	0.001	6.8	0.45	0	0.81	0	No change
-Happy	9	351	282	0.22	0.04-0.39	2.4	0.01	6.0	0.31	0.01	0.91	17	No change
-Disgust	9	311	276	0.25	0.01-0.50	2.1	0.04	15.6	0.05	0.06	0.86	48	No change
-Surprise	8	296	261	0.32	0.12-0.52	3.2	0.002	8.7	0.27	0.02	0.47	20	No change

MS=Multiple Sclerosis HC=Healthy controls, d=Cohen's d, ToM=Theory of mind, CI=Confidence interval

Table-3 Subgroup analyses for social cognition deficis in MS

Test	Study N	d	95 % CI	Z	P	Q	Q (p)	τ^2	I^2 (%)	Q_{bet}
Social cognition	29	0.56	0.42-0.69	8.2	<0.001	48.4	0.001	0.05	42	
Age										1.2
-Matched	21	0.59	0.43-0.75	7.4	<0.001	38.3	0.008	0.06	48	
-Not matched	8	0.44	0.20-0.69	3.5	<0.001	8.9	0.26	0.03	21	
Education										0.05
-Matched	19	0.55	0.42-0.69	8.2	<0.001	20.7	0.29	0.01	13	
-Not matched	10	0.56	0.26-0.86	3.6	<0.001	27.7	0.001	0.15	68	
Depressive symptoms										1.6
-No difference	7	0.45	0.27-0.64	4.8	<0.001	6.5	0.37	0.01	8	
-More in MS	15	0.59	0.35-0.82	4.9	<0.001	33.8	0.002	0.12	58	
Cognition										16.4**
-Impaired	14	0.82	0.65-0.99	9.3	<0.001	15.2	0.29	0.02	15	
-Not impaired	10	0.36	0.17-0.54	3.8	<0.001	11.2	0.26	0.02	20	
Mild/moderate only (disability)										1.3
-Yes	10	0.43	0.25-0.61	4.7	<0.001	11.1	0.27	0.02	19	
-No	12	0.55	0.37-0.73	6.0	<0.001	14.5	0.21	0.02	24	

MS=Multiple Sclerosis HC=Healthy controls, d=Cohen's d, ToM=Theory of mind, ** 0.01>p

Social cognition in multiple sclerosis: a meta-analysis

Emre Bora[1], Serkan Özakbaş[2], Dennis Velakoulis[1], Mark Walterfang[1,3]

Supplement-1 Forest plots of meta-analyses of social cognition measures in MS

Figure S1.1 Forest plot of meta-analysis of social cognition in MS compared to healthy controls

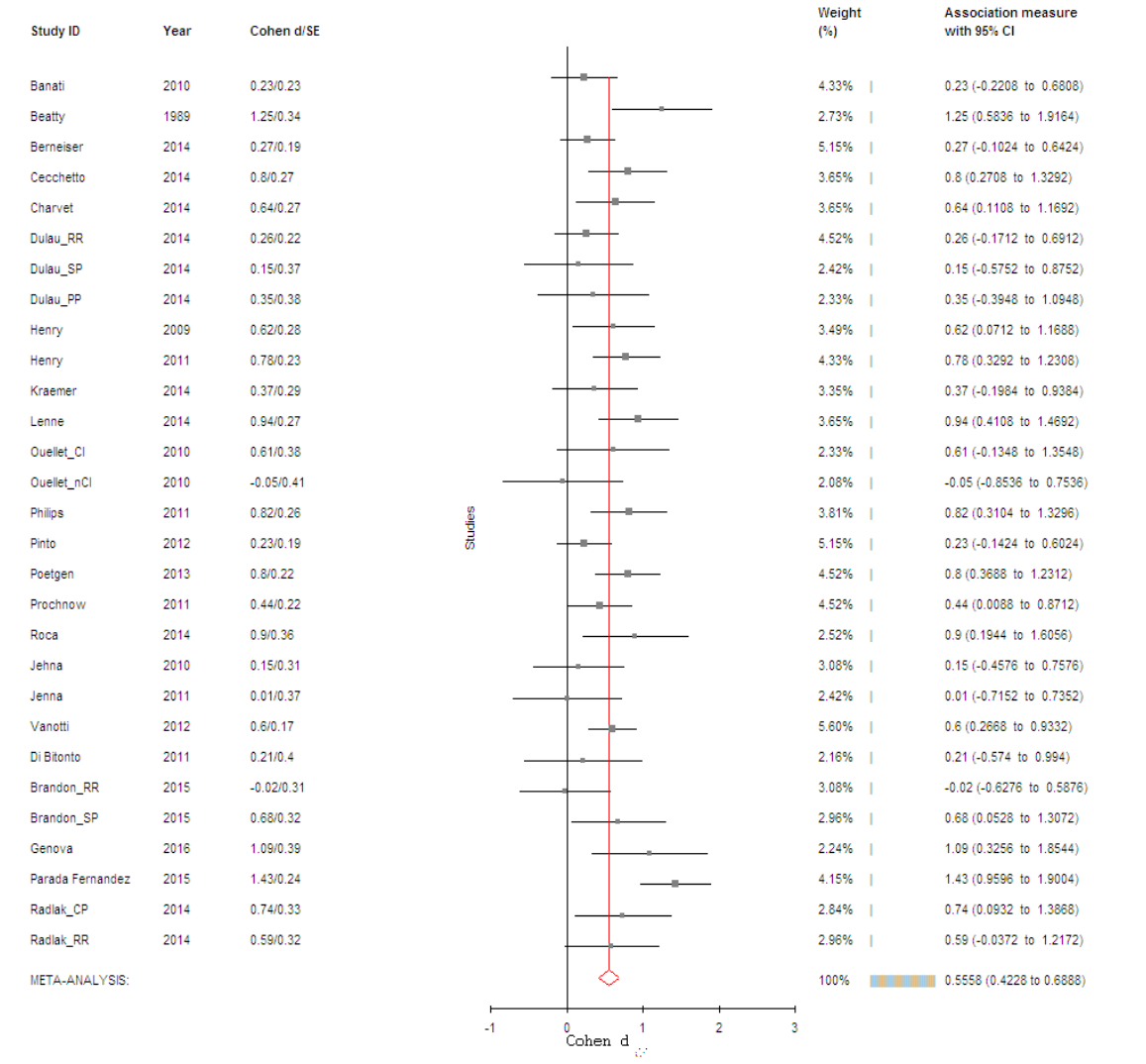


Figure S1.2 Forest plot of meta-analysis of RMET in MS compared to healthy controls

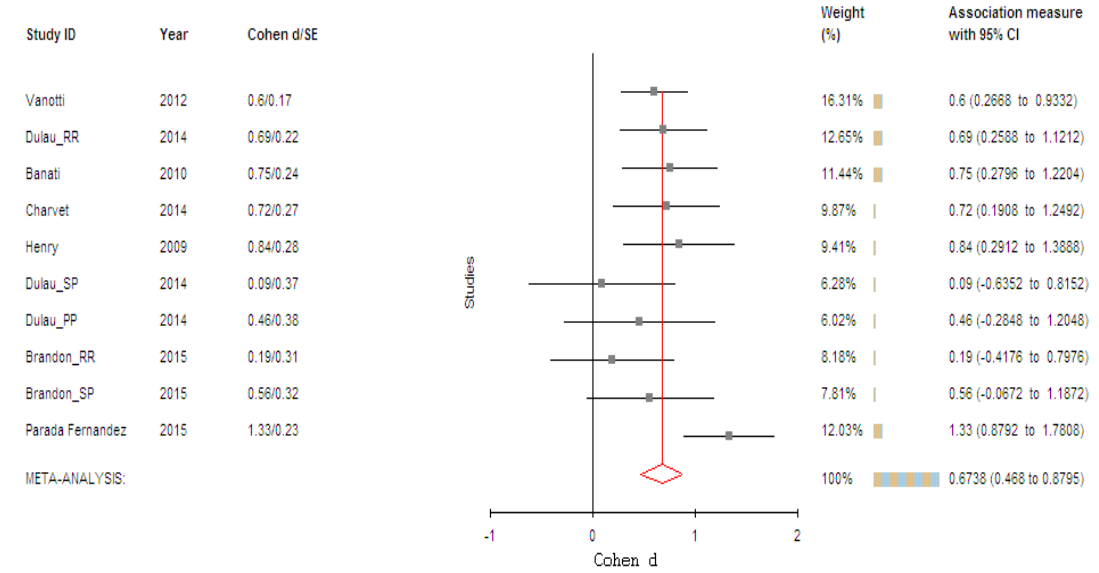


Figure S1.3 Forest plot of meta-analysis of ToM-PT in MS compared to healthy controls

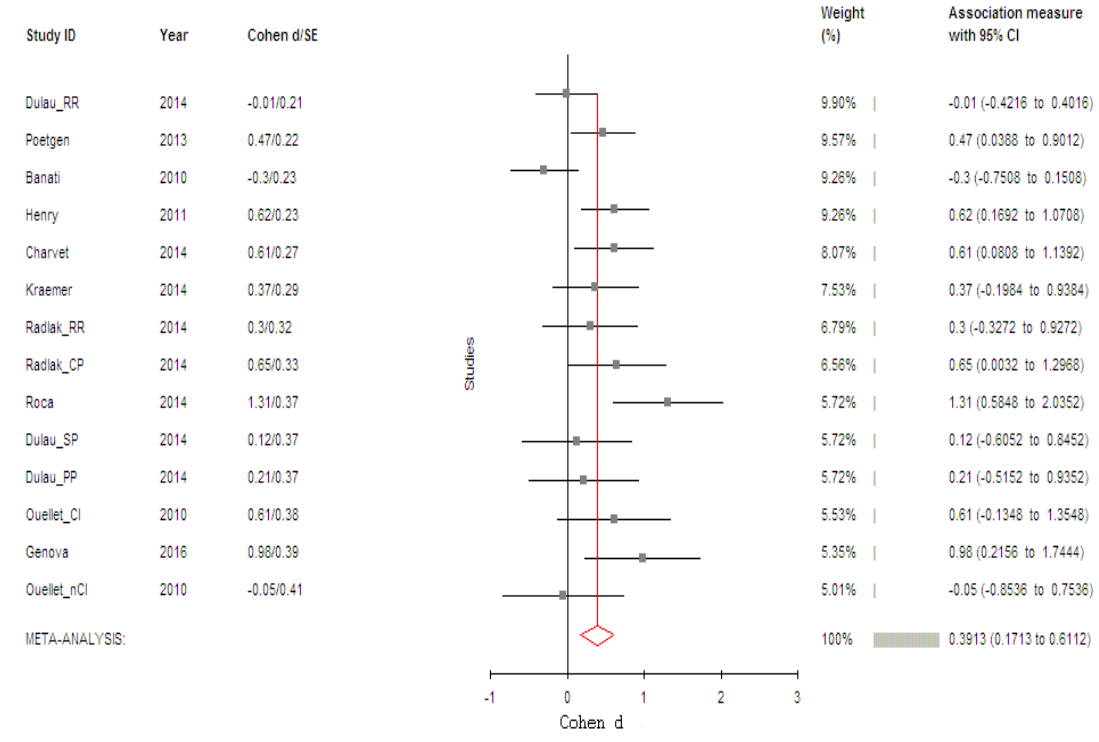


Figure S1.4 Forest plot of meta-analysis of recognition of fear in MS compared to healthy controls

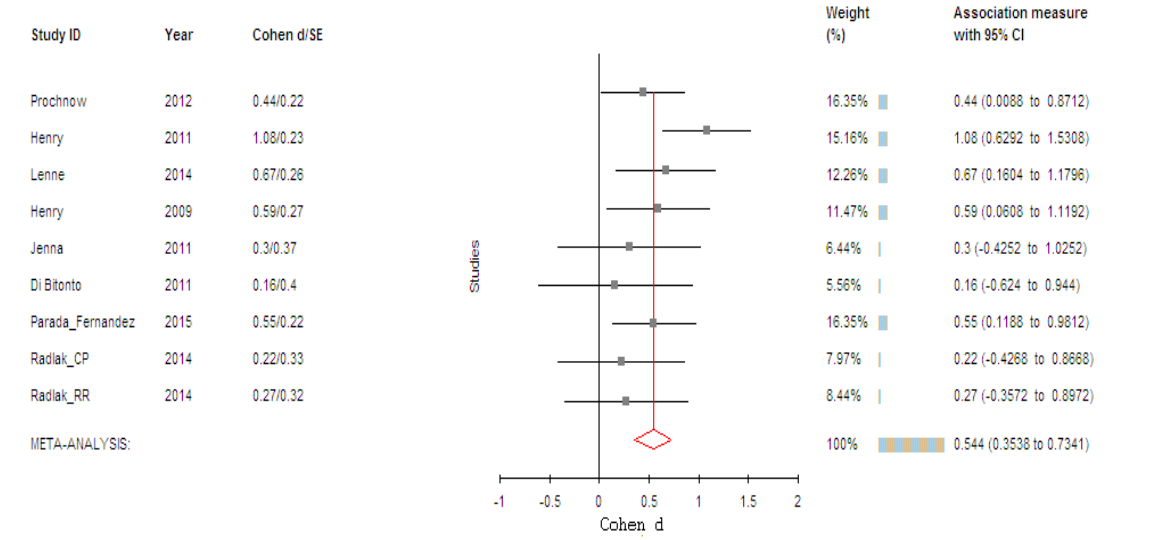


Figure S1.5 Forest plot of meta-analysis of recognition of anger in MS compared to healthy controls

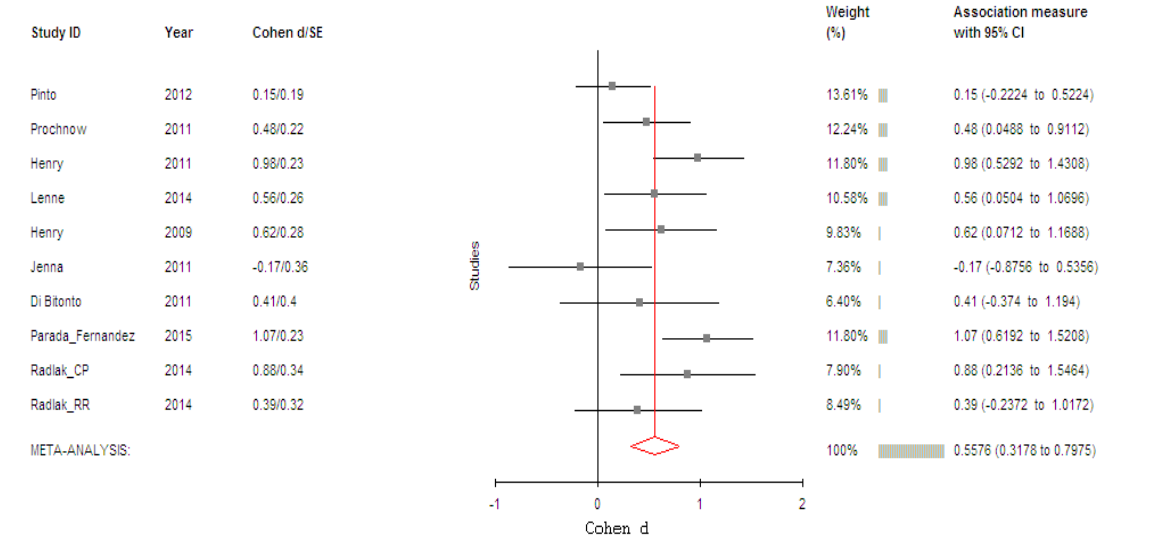


Figure S1.6 Forest plot of meta-analysis of recognition of disgust in MS compared to healthy controls

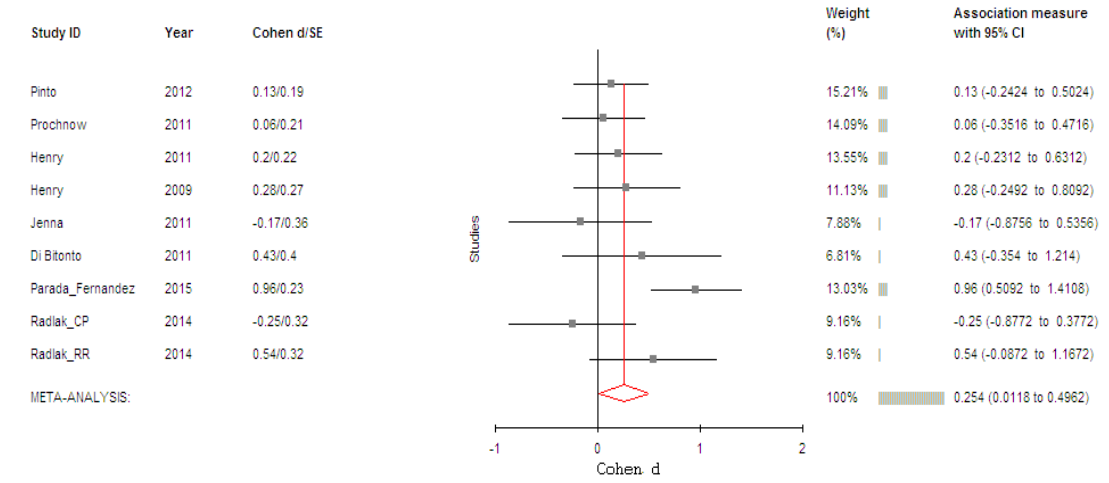


Figure S1.7 Forest plot of meta-analysis of recognition of sad faces in MS compared to healthy controls

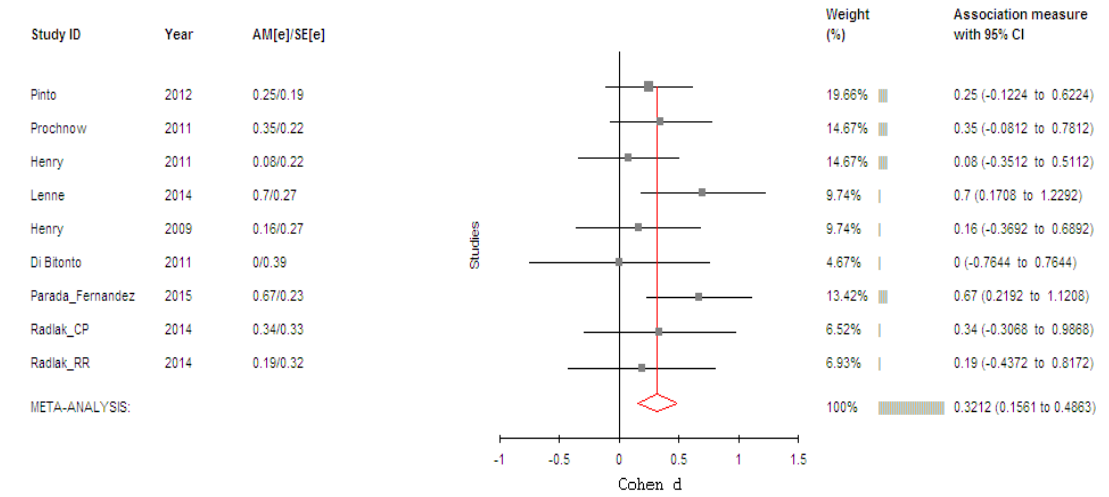


Figure S1.8 Forest plot of meta-analysis of recognition of surprise in MS compared to healthy controls

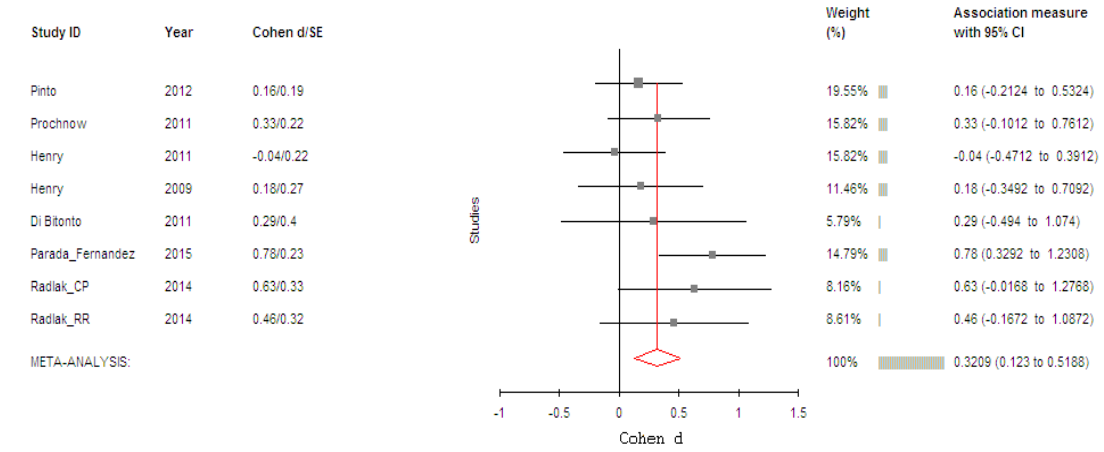


Figure S1.9 Forest plot of meta-analysis of recognition of happy faces in MS compared to healthy controls

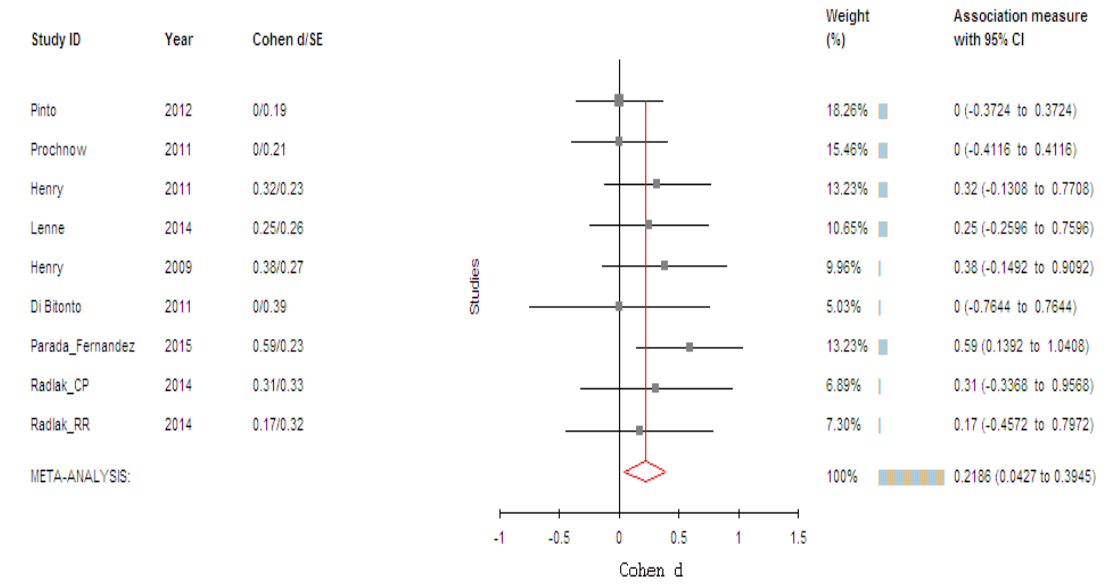
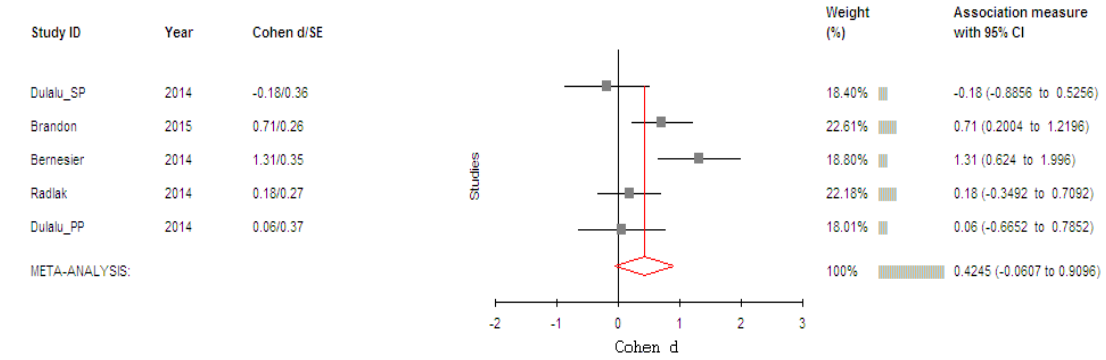


Figure S1.10 Forest plot of meta-analysis of social cognition in chronic progresive vs relapsing remitting MS


Study ID
Year
Cohen d/SE
Weight (%)
Association measure with 95% CI
Dulalu_SP 2014 -0.18/0.36 18.40% -0.18 (-0.8856 to 0.5256)
Brandon 2015 0.71/0.26 22.61% 0.71 (0.2004 to 1.2196)
Bernesier 2014 1.31/0.35 18.80% 1.31 (0.624 to 1.996)
Radlak 2014 0.18/0.27 22.18% 0.18 (-0.3492 to 0.7092)
Dulalu_PP 2014 0.06/0.37 18.01% 0.06 (-0.6652 to 0.7852)
META-ANALYSIS: 100% 0.4245 (-0.0607 to 0.9096)
Studies
-2
-1
0
1
2
3
Cohen d

Social cognition in multiple sclerosis: a meta-analysis

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Supplement-2 Funnel plots of meta-analyses of social cognition measures in MS in comparison to healthy controls

Figure S2.1 Funnel plot for meta-analysis of total emotion recogniton

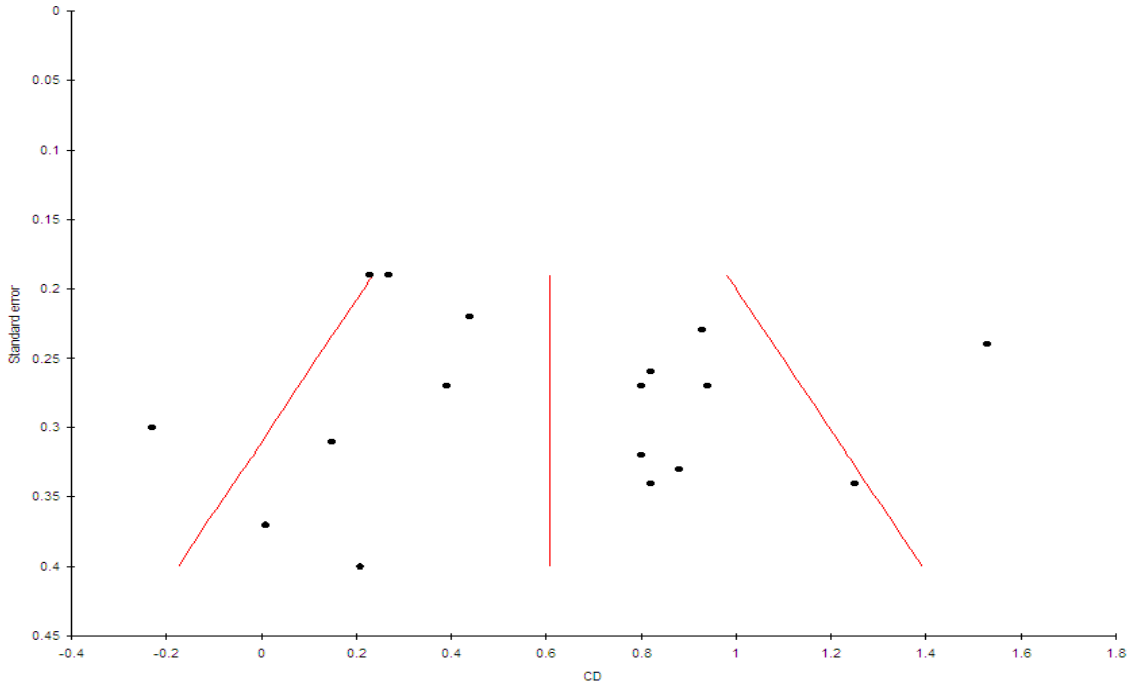


Figure S2.2 Funnel plot for meta-analysis of ToM

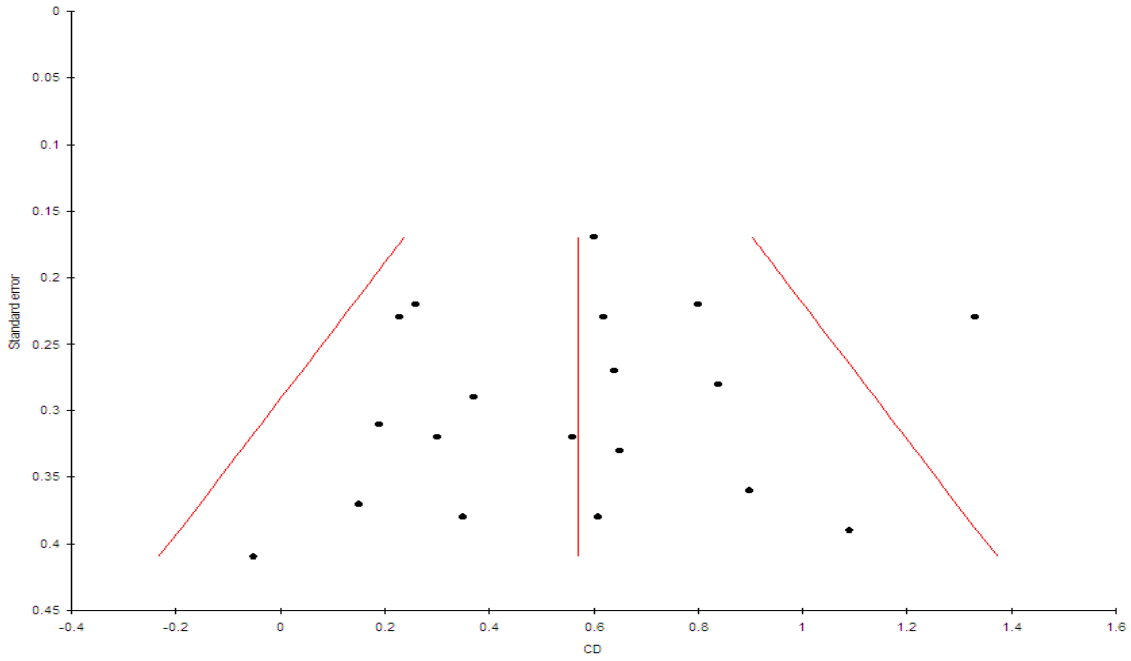


Figure S2.3 Funnel plot for meta-analysis of pooled social cognition score

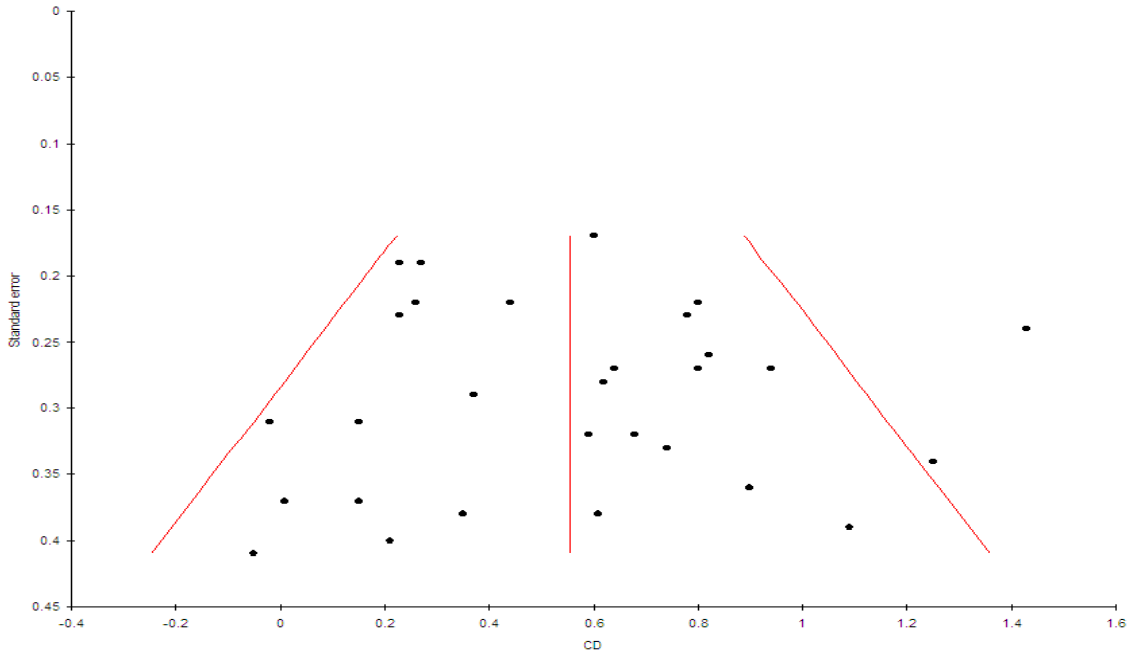


Figure S2.4 Funnel plot for meta-analysis of RMET

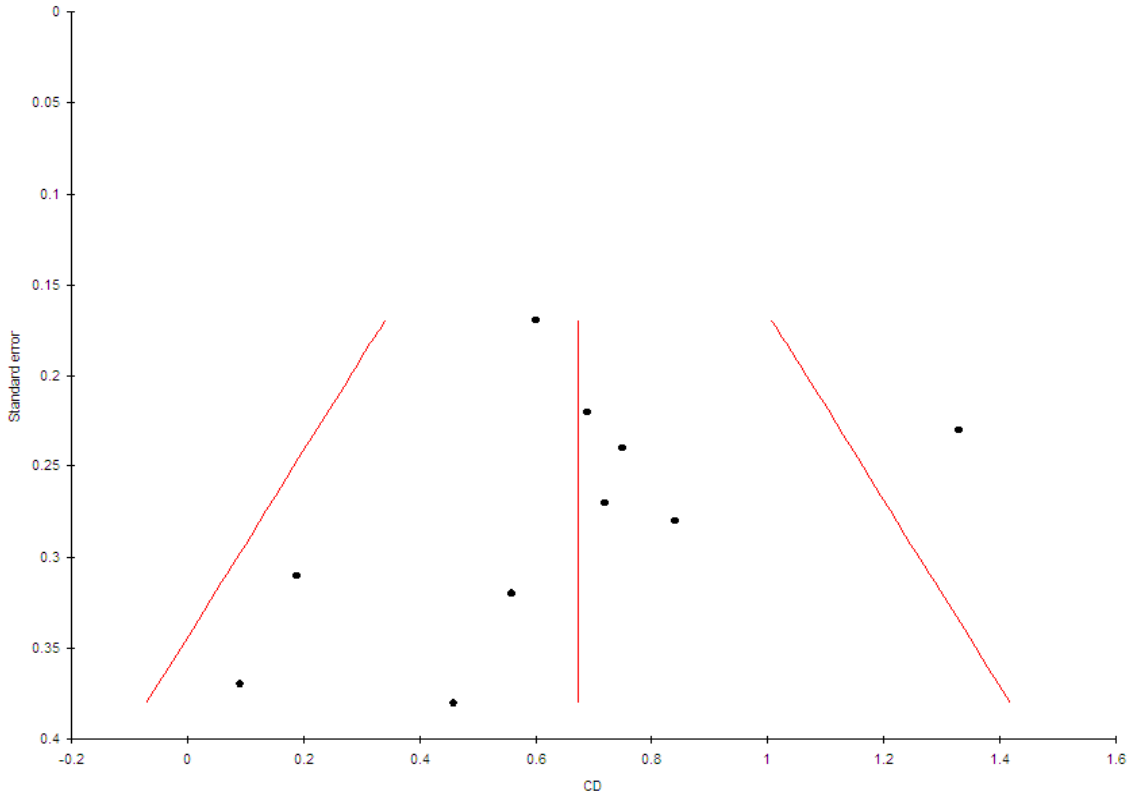


Figure S2.5 Funnel plot for meta-analysis of ToM-PT

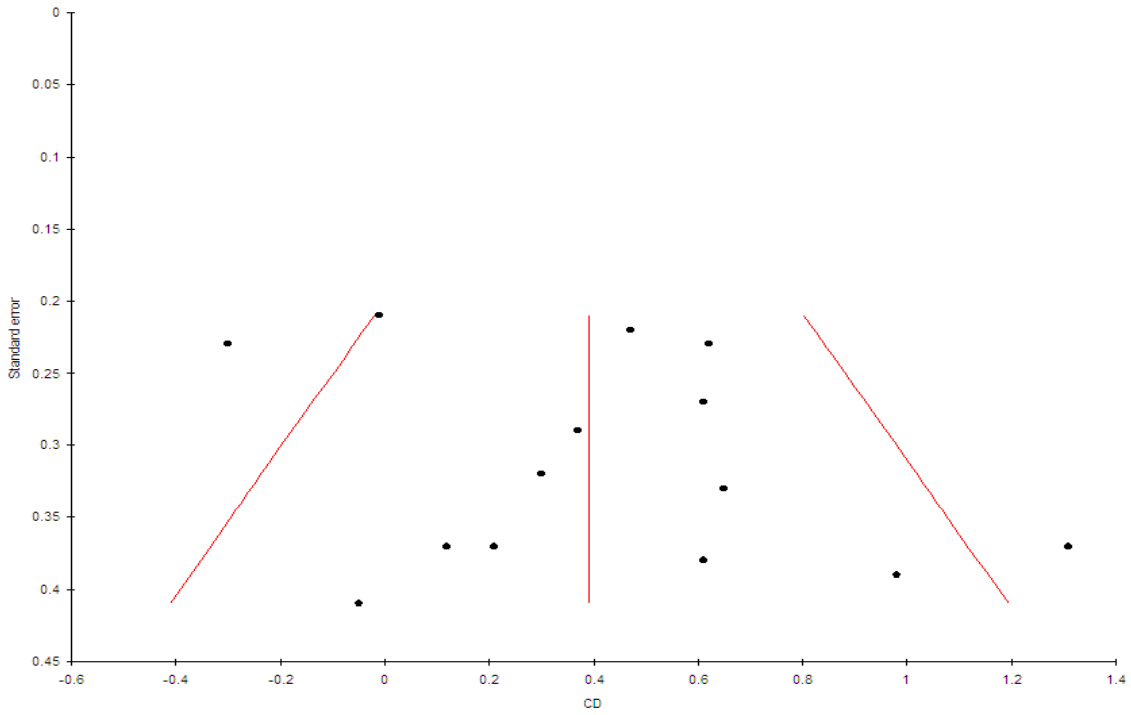


Figure S2.6 Funnel plot for meta-analysis of faux pas recognition test

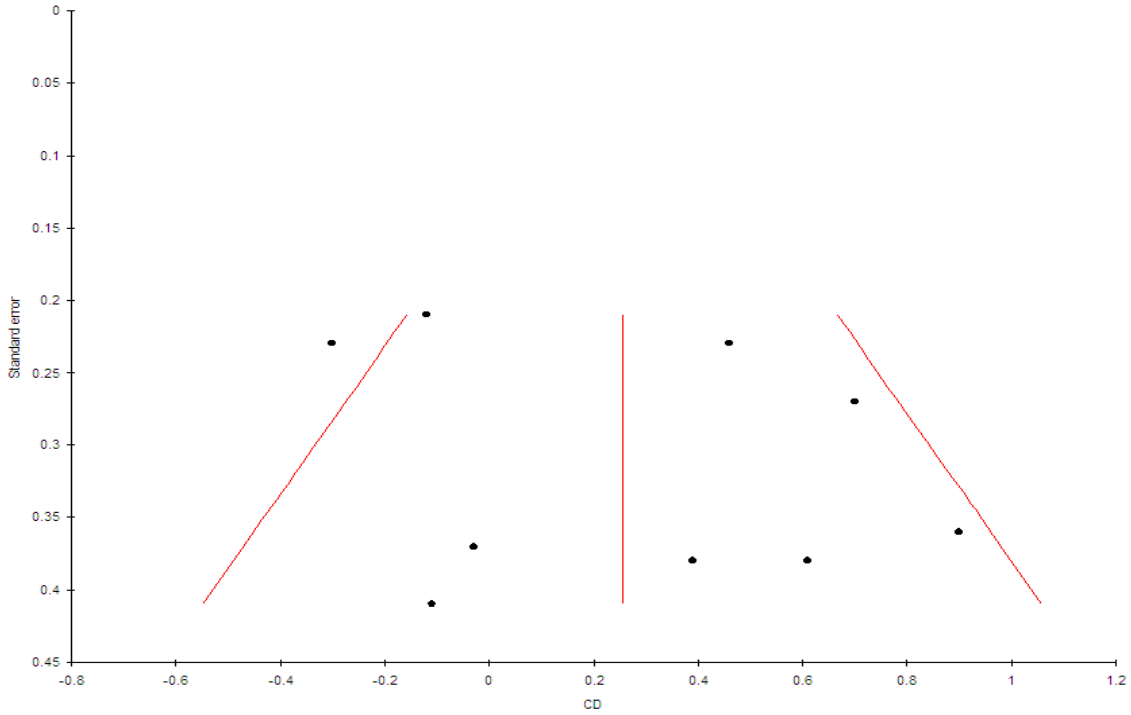


Figure S2.7 Funnel plot for meta-analysis of facial fear recognition

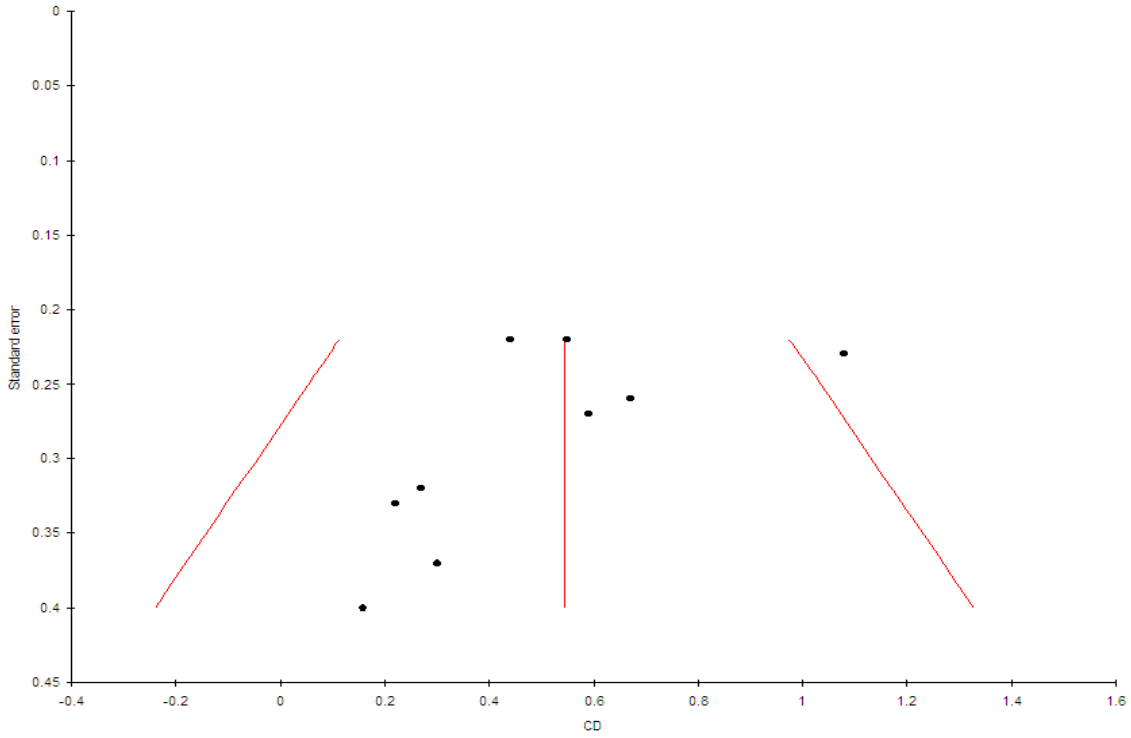


Figure S2.8 Funnel plot for meta-analysis of recognition of angry faces

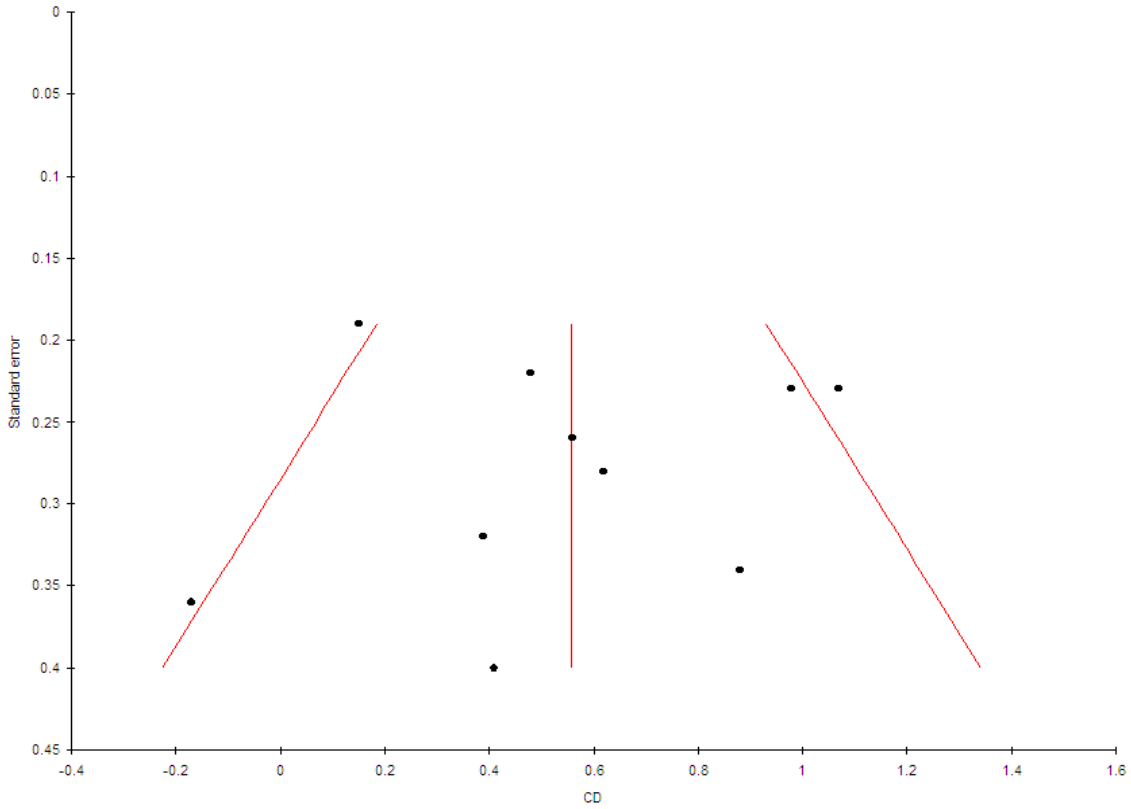


Figure S2.9 Funnel plot for meta-analysis of facial disgust recognition

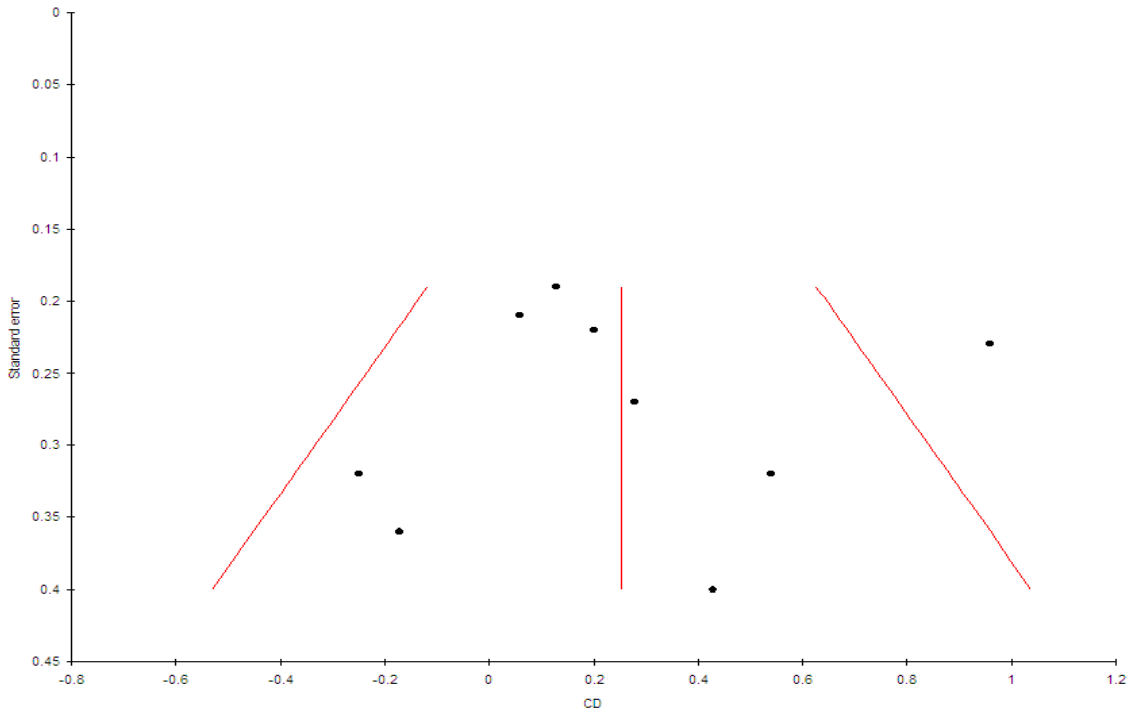


Figure S2.10 Funnel plot for meta-analysis of recognition sad faces

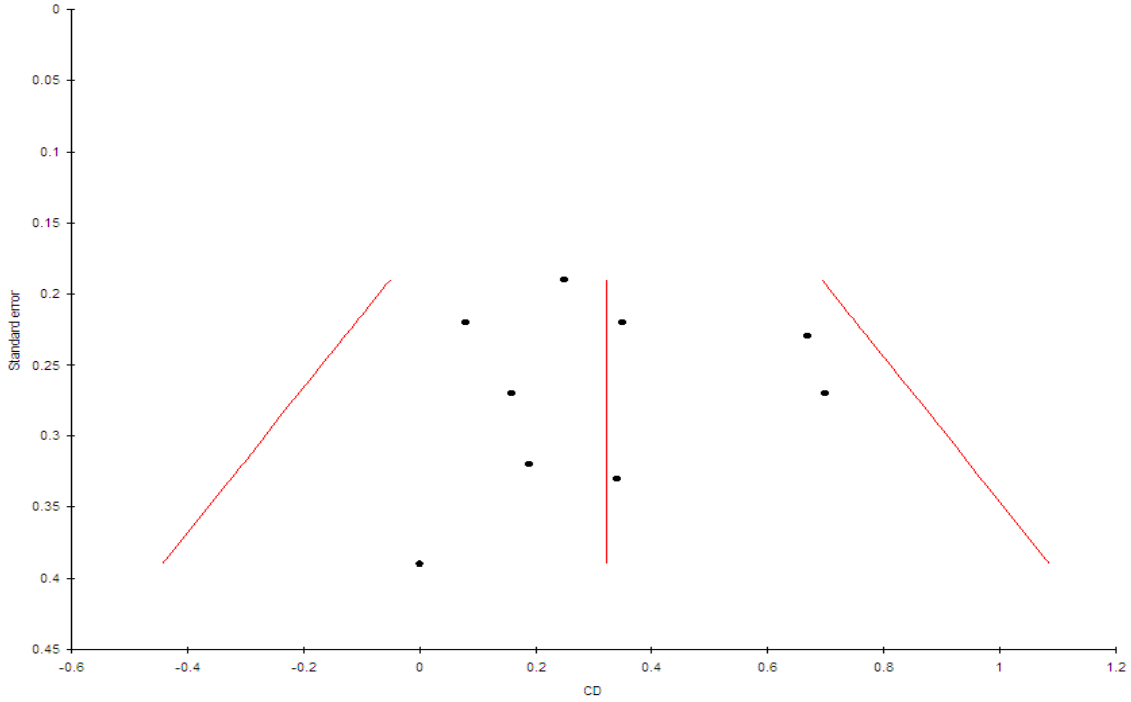


Figure S2.11 Funnel plot for meta-analysis of facial surprise recognition

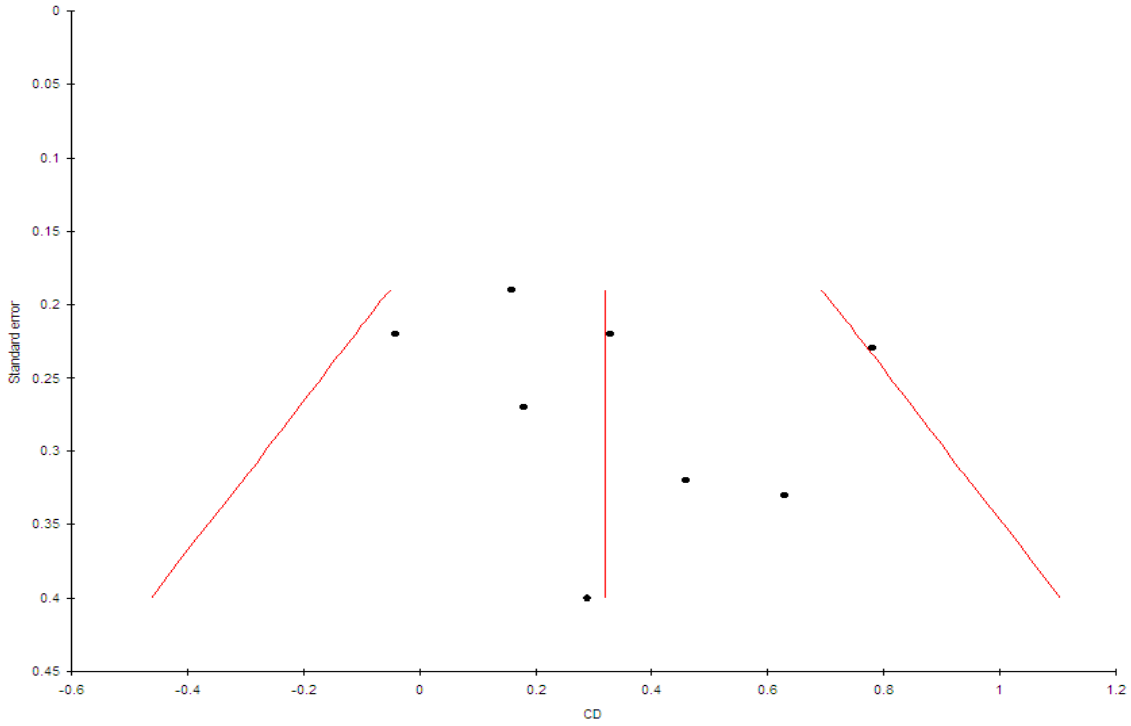
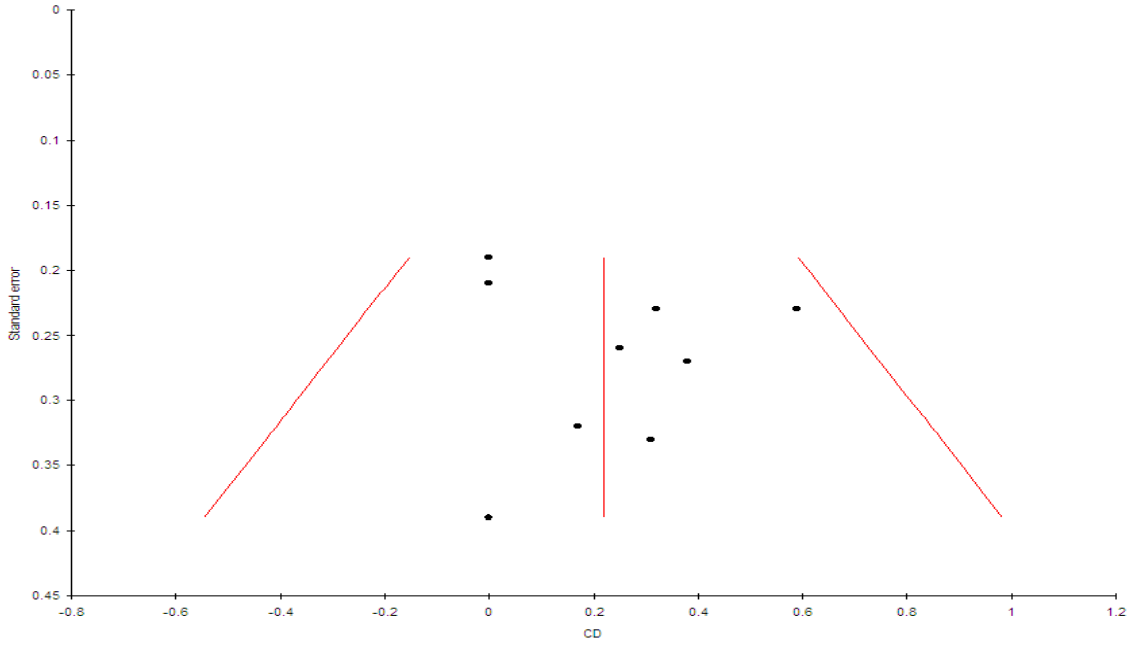


Figure S2.12 Funnel plot for meta-analysis of recognition of happy faces



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