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Neural correlates of theory of mind and empathy in schizophrenia: An activation likelihood estimation meta-analysis

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1. Introduction

Schizophrenia is a severe psychiatric disorder that seems to arise from neurodevelopmental abnormalities caused by gene-environment interactions (Kahn and Sommer, 2015; Kahn et al., 2015; Owen et al., 2016). Several authors have suggested that social cognitive deficits are associated with psychotic symptoms (Fett et al., 2013; Frith and Corcoran, 1996) and predict impaired social functioning in patients (Mohnke et al., 2015; van Os et al., 2010). Neuroimaging studies further suggest that social cognition tasks are related in schizophrenia to abnormal activation of brain regions known as the “social brain” (Green et al., 2015). Although several previous studies explored the neurofunctional correlates of subprocesses of social cognition, the fine distinction between two core processes – theory of mind and empathy – has not yet been examined in a meta-analysis of neural correlates. Further understanding of the neural correlates of social information processing in patients with schizophrenia could help us to identify interesting targets for future therapeutic interventions in psychosocial rehabilitation programs.

Social cognition comprises a set of skills that help us process, store and apply information about social situations (Sebastian et al., 2012), which leads to optimal social functioning (Abu-Akel and Shamay-Tsoory, 2011; Walter et al., 2009). Theory of mind (TOM), or mentalizing, is a central component of social cognition. It is the ability to attribute mental states such as intentions, beliefs or emotions to other people and to understand that these states may be different from our own (Premack and Woodruff, 1978). In neuroimaging studies, TOM appears to be robustly related to activation in the medial prefrontal cortex (mPFC) and bilateral posterior temporoparietal junction (TPJ), which are organized into the core “social brain” network (Schurz et al., 2014). Another key component of social cognition is empathy, a complex psychological construct that comprises the ability to identify other people’s emotions, feel them, and adopt related social

behavior (Carré et al., 2013). Three main components of empathy have been distinguished in the literature: cognitive, affective, and behavioral empathy (Bensalah et al., 2015). Cognitive empathy relies on the affective perspective taking that enables us to understand other people's emotional states (Sebastian et al., 2012). Affective empathy refers to the ability to share emotional states with persons who are interacting socially with us (Bensalah et al., 2015), and seems to be underpinned by emotional contagion and, to a lesser extent, by emotional disconnection (Carré et al., 2013; Singer and Lamm, 2009). Finally, behavioral empathy refers to the ability to adopt appropriate prosocial behavior in response to others' affective states, for example, to comfort someone who is crying (Bensalah et al., 2015). The complex relationship between empathy and TOM is illustrated in Figure 1.

<Figure 1 about here>

Although empathy and TOM are closely related psychological concepts, it has been shown that they differ at the psychopathological (Shamay-Tsoory et al., 2010) and anatomical levels (Mazza et al., 2007; Shamay-Tsoory et al., 2006; Shamay-Tsoory et al., 2007b; Shur et al., 2008). Although the neural networks underlying TOM and empathy partially overlap, exploration of their distinct neural correlates in healthy participants has shown that TOM recruits posterior “social brain” regions, comprising the precuneus and cuneus and bilateral middle and superior temporal gyrus (MTG and STG), while empathy activates anterior brain regions, including the mPFC, cingulate cortex, insula, and caudate nucleus (Bodden et al., 2013; Saxe et al., 2007; Schlaffke et al., 2015; Sebastian et al., 2012).

For several reasons, schizophrenia can be considered a particularly interesting model for studying how emotional content changes brain activation during the attribution of mental states to other people. First, schizophrenia is characterized by impaired social functioning (Brüne et al., 2008; Fett et al., 2011; Green, 2016; Maat et al., 2012), which appears to be correlated with

abnormal activation of the mentalizing network (Bosia et al., 2012; Brunet-Gouet and Decety, 2006; Fujiwara et al., 2015; Green et al., 2015; Jáni and Kašpárek, 2018; Kronbichler et al., 2017; Mohnke et al., 2015). Second, patients with schizophrenia display a well-documented deficit affecting both TOM (Bora et al., 2009; Chung et al., 2014; Green et al., 2015; Lee et al., 2015; Mohnke et al., 2015; Savla et al., 2013) and empathy (Derntl et al., 2009; Fujino et al., 2014). Nevertheless, there is still some controversy regarding the attribution of emotions compared to the attribution to beliefs in people with schizophrenia. In some studies, emotional attribution to others is described as less impaired than belief attribution in patients (Okruszek et al., 2018), while other studies suggest the contrary (Green et al., 2015; Shamay-Tsoory et al., 2007a). Several neuroimaging studies have shown that schizophrenia is characterized by a decrease in volume (Hooker et al., 2011; Koelkebeck et al., 2013; Maat et al., 2016) or metabolism (Benedetti et al., 2009; Brüne et al., 2011; Lee et al., 2011; Mier et al., 2016) in the mentalizing brain areas. Finally, two recent coordinate-based meta-analyses suggested that schizophrenia is associated with abnormal brain activation during TOM (Kronbichler et al., 2017) and emotional recognition (Jáni and Kašpárek, 2018) tasks. Nevertheless, no previous meta-analyses have compared brain activation during TOM and empathy tasks in this population.

In this study, our aim was to further explore the TOM and empathy neural networks in individuals with schizophrenia. Given the limitations of the paradigms used in neuroimaging studies to explore these different processes, we assigned the attribution of intentions or beliefs to others to TOM, which corresponds to cognitive TOM in the strict sense of the term (Figure 1), while the processes that involve affective perspective taking were assigned to empathy. In particular, we attempted to answer two unresolved questions: (1) How does emotional content affect brain activation during mentalization processing in people with schizophrenia? (2) Is there any brain area that is abnormally activated in both cognitive TOM and empathy processing in

patients with schizophrenia? Based on the existing literature, we expected to find abnormal brain activation of posterior regions (posterior superior temporal sulcus (STS), precuneus, cuneus) during TOM tasks and of more anterior regions of the prefrontal cortex (ventromedial PFC, dorsolateral prefrontal cortex (DLPFC)) and insula during empathy tasks. We also expected that some brain structures would be shared by the TOM and empathy networks, such as the TPJ and mPFC. We hypothesized that abnormal brain processing of mental attribution in schizophrenia could overlap in the mPFC, TPJ, posterior cingulate cortex and precuneus.

2. Material and methods

2.1 Data used for meta-analysis: Literature search and selection

We searched the MEDLINE, PsycINFO, Embase, and Current Contents databases for functional neuroimaging studies that investigated the neural correlates of TOM and empathy in patients with schizophrenia compared to healthy controls (HC). We also searched relevant references from the retrieved papers to complete our database. We used the following keywords: theory of mind or mentalizing or false belief or perspective taking or empathy or empathic AND fMRI or PET or brain AND schizophrenia or schizophrenic or psychosis. Our meta-analysis procedure adhered to the PRISMA Statement guidelines, with inclusion and exclusion criteria determined a priori and a systematic review of the selected articles by two authors before inclusion by consensus (Figure 2). Data were extracted independently by the first author and reviewed by two other authors. The 7-item Newcastle-Ottawa Scale for case-control studies was used to assess the risk of bias in included studies (Wells et al., 2009). For each identified bias, we considered how it might have affected the findings and a consensus was reached between all three authors. Moreover, we conducted this meta-analysis in accordance with the “Ten simple rules for neuroimaging meta-analyses” drafted by the developers of the three main algorithms for

coordinate-based meta-analyses (Müller et al., 2018). This meta-analysis is registered in the PROSPERO database under the number CRD42019127308.

<Figure 2 about here>

The inclusion criteria accepted whole-brain neuroimaging studies that compared patients with schizophrenia to HC subjects, with coordinates reported in the MNI or Talairach system, published between January 2000 and December 2018. To be included, the study needed to satisfy the following requirements: (1) All neuroimaging paradigms were based on the contrast between experimental conditions related to attribution of intentions/beliefs (TOM), on one hand, and emotional states (empathy), on the other, in social contexts and control conditions. We included all types of task supports (cartoons, video and audio materials). (2) The schizophrenia diagnosis for patients was based on DSM or CIM criteria. (3) We did not include studies with tasks requiring the attribution of mental states to the self because, even though the activated self-awareness network partially overlaps the social cognition network, it remains structurally and functionally separate in healthy subjects (van Veluw and Chance, 2014) and also in individuals with schizophrenia (van der Weiden et al., 2015), so such studies could have induced bias in our study. Nor did we include emotional recognition tasks because they do not require perspective taking in a social context (Fakra et al., 2015; Li et al., 2010; Taylor et al., 2012), and as such cannot be regarded as tapping into TOM or empathy.

We identified studies with experimental tasks that used short cartoons, stories read or listened to, or video content that contrasted a condition requiring intention or belief attribution to others with a control condition as TOM studies. We labeled studies where the participants were instructed to attribute emotional states to others in a social context, with or without “feeling into” the other person’s affective state, as empathy studies. Thus, in the empathy group, we included studies that explored the neural correlates of affective TOM, where the participants were asked to

attribute emotional states to others, and those that required both emotional inference and emotional sharing. These studies used mostly visual, sometimes textual or auditory, stimuli, which conveyed affect-laden social situations that participants watched passively or evaluated on various dimensions. We did not include in this category studies that investigated neural correlates of empathy for pain in schizophrenia (Horan et al., 2016). Although pain processing has an affective dimension that could be considered as an emotion, the neural correlates of pain empathy do not fully overlap the brain network related to empathy usually described in HC (Bzdok et al., 2012) or in schizophrenia (Vistoli et al., 2017; Wojakiewicz et al., 2013). Details on the included studies are provided in Table 1.

<Table 1 about here>

2.2 Activation Likelihood Estimation procedure

We used GingerALE version 2.3.6 (brainmap.org/ale) to run the Activation Likelihood Estimation (ALE) algorithm (Eickhoff et al., 2017). First, the coordinates of the studies reporting activation in the MNI space were transformed into the Talairach space using the “convert foci” option implemented in the GingerALE toolbox (Eickhoff et al., 2012; Eickhoff et al., 2009; Turkeltaub et al., 2012). Then we used the more conservative Turkeltaub ALE Method (Turkeltaub et al., 2012) for the ALE calculation. For each study, peaks were modeled as the center of a Gaussian distribution with an automatically calculated median smoothing filter. We used a cluster-level inference threshold correction algorithm, given that Eickhoff et al. (2012) noted that uncorrected p value thresholds and false discovery rate (FDR) corrected thresholds are not optimal. We used $p < 0.001$ as a cluster-forming threshold and 0.05 for cluster-level inference, as recommended by Eickhoff et al. (2012). The threshold corrected for cluster-level inference sets the cluster minimum volume such that only 5% of the simulated data clusters exceed this size.

We performed three different ALE analyses: (1) “Second-level” analyses were performed from all foci for TOM and empathy contrasts extracted from studies that compared people with schizophrenia to HC. For each included study, we used the reported contrasts between two experimental groups for TOM on one side and empathy on the other. (2) We performed contrast analyses between overall activation in the data set comparing TOM and empathy in both study groups to determine overlapping and non-shared neurological correlates. The contrast study was executed with an FDRpN-corrected p value and 10,000 p value permutations. Minimum cluster size was 10 mm³. Finally, (3) functional meta-analytic connectivity modeling analysis (MACM) was conducted based on the ALE algorithm using the BrainMap database (Laird et al., 2009). This approach investigates whole-brain connectivity patterns by assessing the covariance between regions (Kotkowski et al., 2018; Robinson et al., 2010). First, spherical 12-mm-diameter Regions of Interest (ROI) were created on the peak ALE voxel at clusters identified in the “second-level” analysis. Then, each of the ROIs was seeded into the BrainMap database to find the brain regions with covariant activation. The data were drawn from multiple behavioral domains including cognition, emotion, action, and perception. The MACM analysis used the same cluster-level inference with the cluster-forming threshold at voxel level $p < 0.001$. Finally, contrast analyses were performed on the sets of coordinates identified as coactivated during ROI activation to identify the regions of convergence.

The software labeled the resulting maxima according to the Talairach Daemon Toolbox (Lancaster et al., 1997; Lancaster et al., 2000). All functional convergence maps generated by single and contrast studies were imported into Mango (<http://ric.uthscsa.edu/mango/>) and overlaid on an anatomical template for representation purposes.

3. Results

The literature search yielded a total of 17 studies that we included in the TOM category, with a total of 19 experiments reporting 113 activation foci. A total of 274 patients with schizophrenia were compared to 286 HC. Only one study used PET scanning (Brunet et al., 2003); all the others used fMRI. We included 13 studies in the empathy category, with 16 experiments reporting 70 foci from a comparison of 240 patients and 242 HC. Three studies directly compared empathy and TOM in a population with schizophrenia (Benedetti et al., 2009; Lee et al., 2016; Lee et al., 2010).

The ALE meta-analysis of all foci extracted from TOM studies comparing the schizophrenia and HC groups revealed decreased activation in the patients in a 1408 mm³ volume cluster of the left middle temporal gyrus (Talairach: $x = -47.4$, $y = -69.7$, $z = 13.2$; ALE = 0.02; BA39). Our meta-analysis of foci related to empathy revealed convergence of decreased activation in the schizophrenia group in a 664 mm³ volume cluster of the right inferior frontal gyrus (IFG) (Talairach $x = 47.8$, $y = 25.6$, $z = 9.6$; ALE = 0.02; BA45). Both underactivated regions are shown in Figure 3. No significant cluster of increased activation in patients compared to HC was found in either TOM or empathy tasks.

<Figure 3 about here>

Decreased activation in the left TPJ (BA39) appeared to be specifically related to TOM tasks in a subtraction analysis between the TOM and empathy networks in schizophrenia. The conjunction across the neural network related to TOM and empathy in schizophrenia did not link to any significant cluster.

In the functional MACM, an ROI centered on the right IFG resulted in 439 experiments (6,951 subjects, 8,596 foci) and the ROI on the MTG in 296 experiments (4,311 subjects, 5,481 foci). Both ROI regions showed convergence in the bilateral TPJ, left STG, right fusiform gyrus,

bilateral insula, bilateral DLPFC and left amygdala (Figure 3, in blue, and Table 2). While significant overlap was observed for both ROIs, some region-specific effects emerged from the cluster contrast analysis. Specifically, the right IFG appeared functionally connected to the bilateral insula, anterior cingulate gyrus, supplementary motor area and left hypothalamus (Figure 3, in orange, and Supplementary Table 1), while results for the left MTG demonstrated unique functional connectivity patterns to the posterior right TPJ, precuneus, posterior cingulate gyrus, bilateral posterior cerebellum lobes and left parahippocampal gyrus (Figure 4, in green, and Supplementary Table 2).

<Figure 4 and Table 2 about here>

4. Discussion

In this work, we aimed to compare shared and non-shared brain activation patterns during cognitive TOM and empathy tasks in schizophrenia using a coordinate-based ALE meta-analysis. In addition, MACM of the identified brain regions was done.

Compared to HC, individuals with schizophrenia displayed decreased activation in the left MTG (BA39), which overlaps the TPJ, during TOM tasks, and decreased activation in the right IFG (BA45), which overlaps the middle ventrolateral prefrontal cortex (VLPFC), during empathy tasks. Our results suggest that emotional content impacts brain activation during mental state attribution processing in individuals with schizophrenia. These results provide further evidence that the neural processing that underpins reasoning in social contexts is impaired in patients with schizophrenia.

Brain regions involved in TOM in neurotypical development include the ventral and dorsal mPFC, precuneus, TPJ, temporal pole, medial temporal gyrus, posterior STS and inferior frontal gyrus (Bzdok et al., 2012; Schurz et al., 2014). Activation in the anterior cingulate cortex,

inferior frontal gyrus, precuneus, anterior insula, somatosensory cortex and DLPFC correlates most robustly with empathy in healthy participants (Abram et al., 2017; Bzdok et al., 2012; Das et al., 2012; Fujino et al., 2014; Hooker et al., 2008; Lamm et al., 2011). This brain network is believed to represent one's own and others' emotional states regardless of the actual affective or sensory modality (Fan et al., 2011; Lamm et al., 2011).

In a substantial meta-analysis of the neural correlates of TOM, Schurz et al. (2014) found that the left TPJ was strongly activated in social animation tasks, in which geometrical shapes mimicked intentional or social interaction, and to a lesser extent, in more classical TOM tasks such as false belief and "Mind in the Eyes" tasks. Biervoye et al. (2016) suggested that the left TPJ is critically involved in spontaneous belief inference, given that two patients with left TPJ damage failed on false-belief tasks where no explicit mentalizing instruction was given, while they successfully completed tasks when their attention was explicitly directed to an agent's thoughts or actions. Therefore, the patients with left TPJ lesions were able to inhibit self-perspective in false-belief reasoning, but failed to infer someone else's perspective as such. Interestingly, the opposite pattern of performance was reported in a case of a patient with right lateral PFC lesions, who had a selective deficit in inhibiting self-perspective (Samson et al., 2005). These results of lesion studies, namely decreased activation in the right VLPFC and left TPJ, suggest that ability in both self-perspective inhibition and other's perspective taking is impaired in schizophrenia. In addition, dynamic modeling obtained from data during belief reasoning suggested that the left TPJ also processes self-projections and internally generated information in the autobiographical memory network via input integration from the right TPJ and PFC (Schurz et al., 2017; Schuwerk et al., 2014). Our MACM results indicated strong coactivation between the left and right TPJ during belief/intention attribution and are in line with

previous models of self-reasoning that further suggest that the left TPJ may play a specific role in the automatic awareness of task-relevant information retrieved from memory (Berryhill, 2012).

Regarding the right middle VLPFC (BA45), it appears to be recruited in tasks with decision uncertainty that involve reflexive reorienting and motor inhibition (Levy and Wagner, 2011), while the adjacent anterior insula is claimed to be specifically related to introspective awareness and emotional sharing (Craig, 2009; Kurth et al., 2010). The literature indicates that both VLPFC and anterior insula are abnormally activated in patients with schizophrenia during task-related empathy exploration (Derntl et al., 2012; Lee et al., 2010). Comte et al. (2016) suggested that bottom-up emotion appraisal involves activation of the amygdala and connectivity with the anterior cingulate cortex and DLPFC. Moreover, in their meta-analysis, Lee and Siegle (2012) suggested that the amygdala and lateral PFC were involved in emotion cognition processing, while the dorsomedial PFC has a more integrative role in explicit emotional evaluation. Lee and Siegle also suggested that the insula and rostral anterior cingulate cortex are specifically related to attributing emotions to the self and as such may specialize in introspective emotional experiences, while the STS and TPJ are more specifically related to attributing emotions to others. Nevertheless, unlike previous fMRI studies (Das et al., 2007), we did not find an abnormal pattern of activation in the amygdala during empathy processing in individuals with schizophrenia. It should be noted that our MACM showed the left amygdala to be coactivated with both the right VLPFC and left TPJ. In addition, connectivity studies have reported weaker amygdala-prefrontal coupling in individuals with schizophrenia than in HC (Anticevic et al., 2012; Das et al., 2007), while volumetric studies of schizophrenia revealed no significant correlation between emotional recognition or TOM and amygdala volume (Maat et al., 2016). It could be argued that the previously reported underactivation of the amygdala in schizophrenia is the consequence of decreased inputs from the underactivated prefrontal cortex.

The importance of the right VLPFC and left TPJ in the pathophysiology of schizophrenia is highlighted by the work of Andreou et al. (2018), who demonstrated that the “jumping to conclusions” reasoning bias was correlated with abnormal activation in both the left TPJ and the right VLPFC. Averbeck et al. (2011) had participants with schizophrenia execute two cognitive reasoning tasks related to decision-making and suggested that patients are prone to “jumping to conclusions,” which means that they make decisions without having or fully understanding all the information from their environment. This cognitive distortion is very prevalent in patients with delusions (Langdon et al., 2010). Freeman et al. (2014) suggested that patients with delusions who jumped to conclusions had poorer working memory, lower IQ and lower intolerance of uncertainty, suggesting that this cognitive distortion could be at least partially related to difficulties keeping information in mind.

Importantly, both regions we identified as being abnormally activated in TOM and empathy tasks have also been reported to be crucially involved in auditory-verbal hallucinations in patients with schizophrenia (Moseley et al., 2013). More specifically, decreased connectivity between the left TPJ and the right hemispheric homotope of Broca’s area has been observed in patients with residual auditory-verbal hallucinations (Mondino et al., 2016). Consequently, this abnormal functioning and connectivity between the right VLPFC and left TPJ could be related to positive and cognitive symptoms observed in schizophrenia.

Our MACM analysis also suggests that both left TPJ and right VLPFC are highly interconnected with the right TPJ, bilateral insula, left amygdala and DLPFC, which have been described as core regions of the social brain network (Schurz et al., 2014). They also play an important role in cognitive emotion regulation (Kohn et al., 2014), resting state connectivity (Park et al., 2018) and autobiographical memory (Inman et al., 2018). Our MACM results provide further evidence that schizophrenia may be a dysconnectivity disorder (Stephan et al.,

2009), since inputs from the left TPJ and right VLPFC seem to compromise activity in the whole underlying network implicated in both psychopathology and social cognition.

Unlike Jáni and Kašpárek (2018) and Kronbichler et al. (2017), we did not find any compensatory overactivation during TOM tasks in patients with schizophrenia compared to HC. Note that we limited the selection to TOM studies in which participants were asked to infer other people's intentions/beliefs, while Kronbichler et al. (2017) and Jáni and Kašpárek (2018) included those studies with studies on self-attribution of mental states in their meta-analyses. This could explain the significant overactivation in the dorsal bilateral TPJ they observed in schizophrenia, which was not replicated in our study. The nature of attributed mental states (intention, belief, emotion, preference) could further explain the variability of the reported results. Previous studies have reported inconsistent patterns of TPJ activation during TOM tasks: decreased activation in the TPJ bilaterally in patients with schizophrenia compared to HC (Walter et al., 2009), increased activation in patients' left TPJ (Brüne et al., 2008), or no significant group differences (Brunet et al., 2003). In addition, the heterogeneous tasks used in the various studies may also explain the discrepancy in observed results between meta-analyses.

Surprisingly, when we contrasted the neural correlates of TOM and empathy in schizophrenia, we did not find a convergent cluster, but subtraction analysis suggested that activation in the left TPJ was specifically related to the attribution of intentions/beliefs to others.

From the evolutionary and developmental perspectives, functional asymmetry between brain hemispheres is a pattern that is found in many species. The right hemisphere is often found to be superior at emotion processing (Gainotti, 2018). It has been suggested that the left hemisphere controls behavioral patterns in familiar, routine situations, while the right hemisphere processes potentially dangerous changes in the environment, which involves emotional and face recognition, among other things (Bartolomeo and Seidel Malkinson, 2019). Our results suggest

that this asymmetry is partially lost in schizophrenia, as the core regions involved in social information processing, with and without emotional content, are underactivated.

In light of the data from recent neuroimaging studies of schizophrenia, our work provides further arguments supporting the conceptualization of schizophrenia as a dysconnectivity disorder, with a particular focus on the functional integration of brain areas into networks. Thus, here we suggest that impairments affecting two core regions result in impaired mental state attribution in schizophrenia: the left TPJ for intention/belief attribution and the right VLPFC for emotion attribution to others. Abnormal activation of these regions may also be implicated in the maintenance of positive psychotic symptoms such as verbal-auditory hallucinations and in “jumping to conclusions” biases in evidence gathering from the environment. Therefore, specific targeting of the left TPJ and right VLPFC, particularly by neuromodulation techniques, could help mitigate poor social functioning in this population.

4.1 Limitations and conclusion

Although the strength of ALE meta-analysis is its mapping of the most consistently activated brain areas that exceed the statistical threshold for differences in experimental procedure, analysis technique and sample size between studies, some limitations should be acknowledged. We made direct use of the reported neural coordinates of the contrasts between groups in each included study, so some less-reported foci may have been filtered out. Our meta-analysis is based on the available literature and hence may be affected by the potential publication bias against null results. Furthermore, tasks used to assess neural correlates during emotion and intention/belief attribution may suffer from limited ecological validity. In particular, the frequent use of cartoon visual tasks with artificial social context scenarios may have systematically overestimated the involvement of cognitive versus emotional processes even in tasks classified as empathy-related. Therefore, future neuroimaging studies should address two

main questions: How does emotional content interact with the intention/belief attribution network? And how are bottom-up and top-down processes synchronized? In addition, future studies should strive to use more ecological affective and cognitive TOM tasks to explore network activation in scenarios that are closer to real-world social interaction. An overlapping sample in two of the studies examined (Mier et al., 2016; Mier et al., 2010) was taken into account by two separate analyses with data from each study removed. The results obtained in that way overlapped with the results reported in the meta-analysis.

In conclusion, our findings suggest that people with schizophrenia may not have fully functionally specialized neural networks for inferring other people's mental states. Future studies on social cognition in schizophrenia should use more ecological tasks to address the question of how emotional content affects the attribution of mental states to other people in this population. Finally, therapeutic approaches that target the left TPJ and right VLPFC should be tested in future studies of psychosocial rehabilitation in people with schizophrenia.

Conflict of interest

None of authors has conflicts of interest to declare.

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Figure 1: Relationship between empathy and theory of mind based on the models described by Sebastian et al. (2012), Carré et al. (2013) and Bensalah et al. (2015).

A brief definition of each process is provided. Briefly, inferring beliefs and intentions relies on cognitive perspective taking and refers to cognitive TOM. Inferring emotions will solicit three psychological processes: emotional contagion, emotional disconnection and affective TOM. Affective perspective taking makes a connection between emotional disconnection and affective TOM, and refers to cognitive empathy, while emotional contagion refers to affective empathy. Finally, in order to adopt appropriate prosocial behavior, cognitive and affective empathy and also TOM are necessary. A strong, evidence-based relationship between processes is represented by an unbroken line. Color is used for representation purposes. Neural correlates specifically activated during each psychological process are reported, as are three brain regions that are always activated during mental state attribution: the precuneus, bilateral TPJ and posterior STS, core structures of social brain.

TOM: theory of mind; PFC: prefrontal cortex, TPJ: temporo-parietal junction, STS: superior temporal sulcus

Figure 2: PRISMA flow diagram of literature search for review.

Figure 3: Functional clusters from comparison analysis between theory of mind and empathy networks in patients with schizophrenia and healthy controls, showing significant neurofunctional convergence of decreased activation in individuals with schizophrenia in the right ventrolateral prefrontal cortex (VLPFC, BA45) for empathy tasks (in orange) and in the left posterior temporo-parietal junction (TPJ, BA39) for TOM tasks (in green). Mask dimensions = 80 x 96 x 70; Number of within-brain voxels = 226,657; Number of foci = 113 (TOM), 70 (empathy); Number of experiments = 19 (TOM), 16 (empathy); Maximum ALE score = 0.02; Threshold method =

Cluster-level inference; Thresholding value = 0.001; Thresholding permutations = 1,000; Cluster-forming value = 0.05. Figure created using Mango (<http://ric.uthscsa.edu/mango>).

Figure 4: Coactivation patterns obtained from meta-analysis connectivity modeling with the right inferior frontal gyrus (IFG, in orange) and left middle temporal gyrus (MTG, in green). Brain regions that coactivated with both right IFG and left MTG are indicated in blue. Maps thresholded at $p < 0.001$, FDRpN-corrected. Figure created using Mango (<http://ric.uthscsa.edu/mango>).

Table 1: Summary of theory of mind (TOM) and empathy (EMP) studies included in the meta-analysis, presenting the neuroimaging task contrast used by the authors, the number of participants included and the main study group characteristics.

Table 2: Meta-analytic connectivity modeling (MACM) results for the conjunction analysis, showing brain regions coactivated with the right IFG and left MTG. Coordinates are reported in Talairach space.

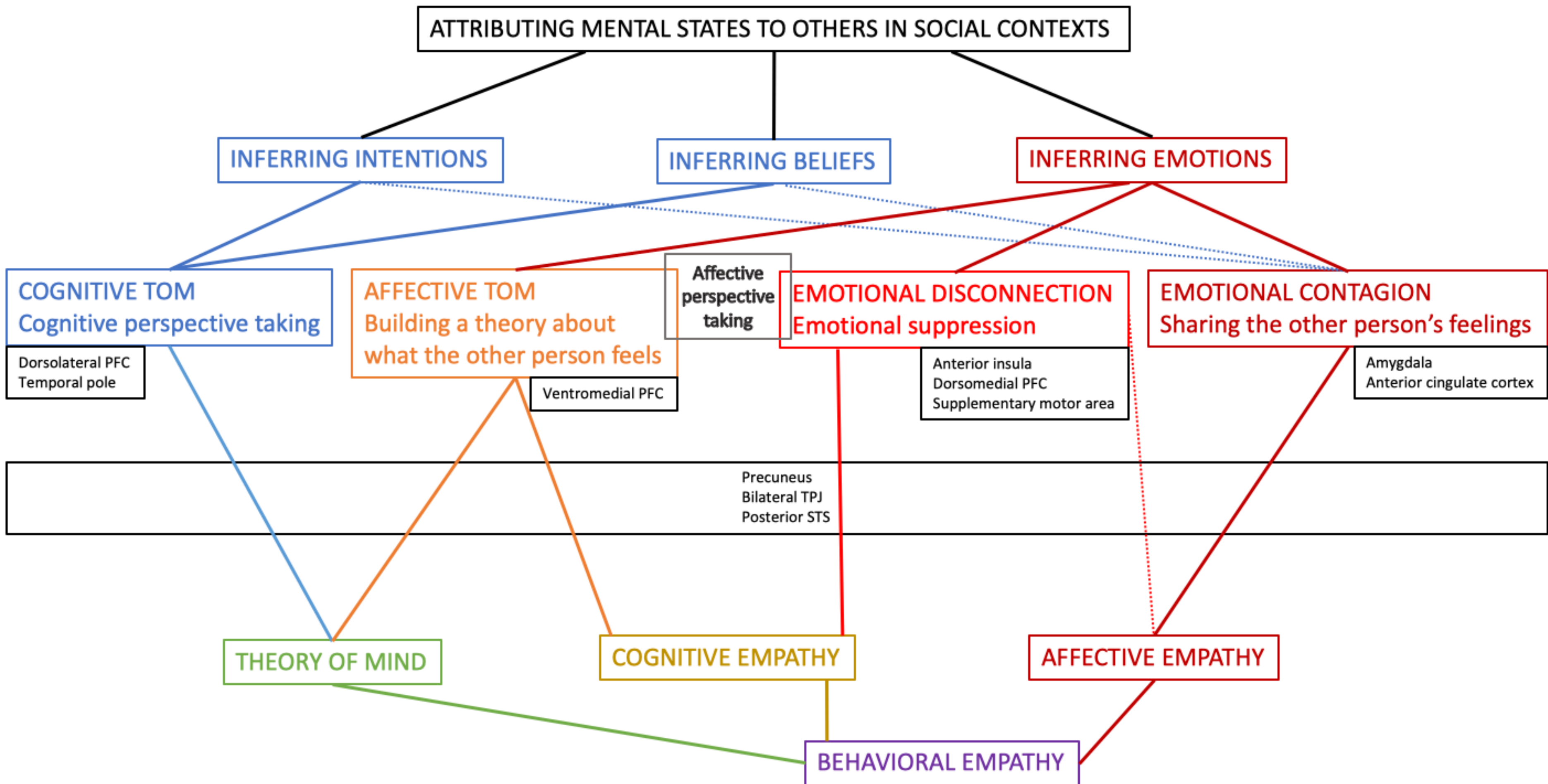
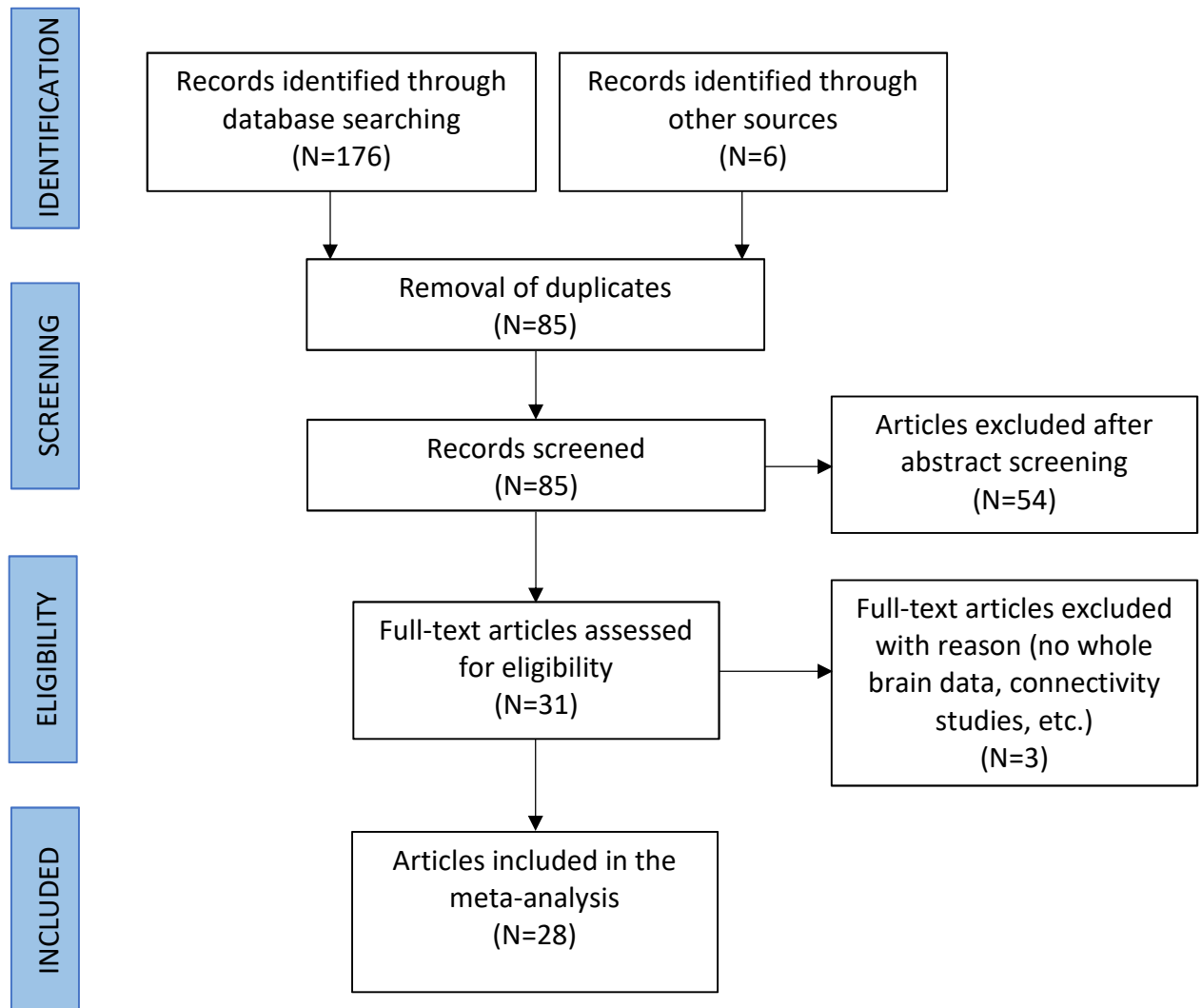


Figure 1



SCZ<TE

L

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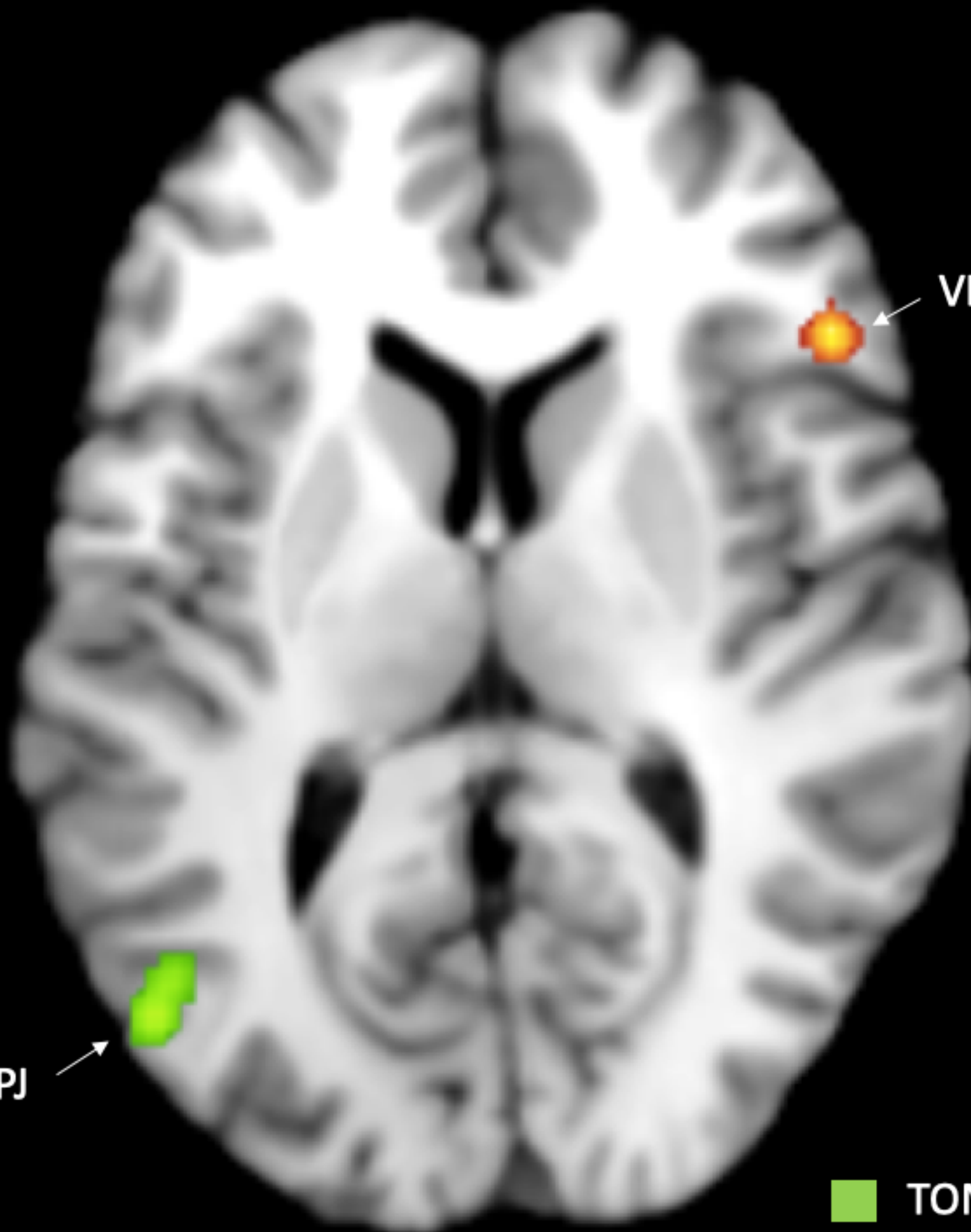
VLPFC

TPJ

Z=10

TOM tasks

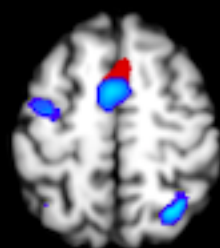
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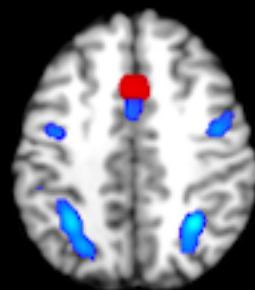
MACMs



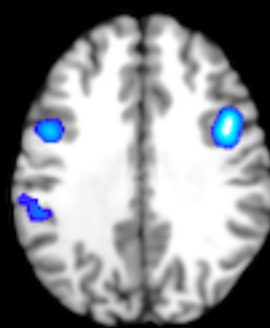
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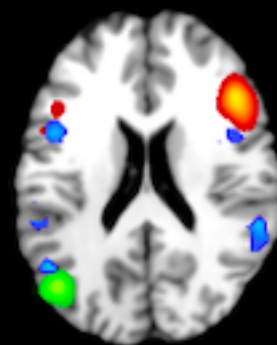
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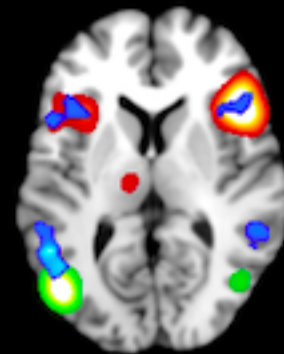
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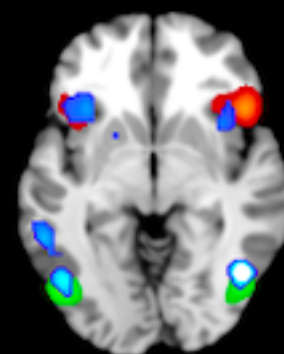
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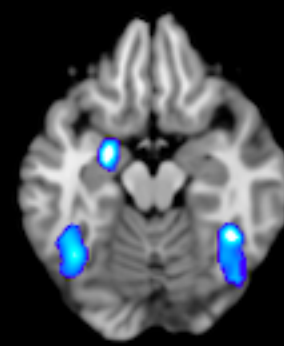
$z = 20$



$z = 9$



$z = -2$



$z = -13$



Reference / Experimental Group	Experimental and Control Task	Neuroimaging	Participants	
		Design	<i>Study Group (N)</i>	<i>Controls (N)</i>
		<i>p-value (correction)</i>	Mean: Age/Education level/IQ/PANSS pos.; neg. level/IQ	Mean: Age/Education
1. Russell et al. (2000) / TOM	Mind in the eye task: view photographs of eyes and choose one of 2 proposed words that best describes the mental state reflected in the photographed eyes. In the control condition, participants had to determine the gender of the photographed eyes.	fMRI 1.5T event-related $p < 0.01$ (uncorrected)	SCZ (5) 36/11/100/NA Illness duration (years): 13 ± 7	HC (7) 40/16/116
2. Brunet et al. (2003) / TOM	View a cartoon story and predict what will happen based on protagonists' intentions (no false belief) with choice of appropriate ending from three proposed options. In the control condition, the cartoon story concerned physical causality involving characters or objects.	H2O ¹⁵ PET Scan Block $p < 0.01$ (uncorrected)	SCZ (7) 31/NA/111/17.8; 19.5	HC (8) 23.3/NA/119
3. Lee et al. (2006) / EMP	Read a short vignette with protagonists in social interaction (empathy or forgiveness scenario compared to baseline social reasoning scenario as control), then make 5 serial judgments.	fMRI 1.5T event-related $p < 0.005$ (uncorrected)	SCZ (14) 31.7/NA/109.6/NA Chlorpromazine-equivalent dose (mg/day): 406.4 ± 205.6 Illness duration (years): 9.8 ± 5.4 Assessment before and after recovery	HC (14) 30.5/NA/112.3
4. Brüne et al. (2008) / TOM	View a 4-picture cartoon story of protagonists in social interaction. In TOM condition, participants had to respond to a question about the protagonist's intentions vs. physical characteristics (e.g., color of t-shirt). In non-TOM condition, the pictures were presented in jumped order.	fMRI 1.5T Block $p < 0.002$ (uncorrected)	SCZ (9) 29/NA/94/16.7; 15.7 Chlorpromazine-equivalent dose (mg/day): 244.44 (mean) Illness duration (years): 3 (from 0.5 to 13)	HC (13) 26.5/NA/126

5. Walter et al. (2009) / TOM	View a cartoon story showing 2 persons in social interaction. One is making a communicative gesture (pointing to a bottle to request it). Choose a logical ending from 3 available options. In the control condition, a cartoon story involved objects in a physical causality relation.	fMRI 1.5T event-related $p < 0.001$ (uncorrected)	SCZ (12) 29.5/12.4/NA/17.75; 19.41 Illness duration (years): 6.3 ± 5.2	HC (12) 24.75/12.3/NA
6. Benedetti et al. (2009)/ TOM and EMP	View a cartoon story and predict what will happen based on protagonists' intentions or emotions (no false belief) with appropriate ending choice from 2 proposed options. In the control condition, the cartoon story concerned physical causality.	fMRI 3T block $p < 0.001$ (uncorrected)	SCZ (24) 37.2/NA/NA/16;21.6 Chlorpromazine-equivalent dose (mg/day) 357.81 ± 256 Illness duration (years): 12.7 ± 7	HC (20) 35.1/NA/NA
7. Park et al. (2009) / EMP	Watch a short video where a human avatar narrates an event with emotional prosody (happy, angry or neutral). Participants had to infer if the certain or uncertain statement presented after the video was congruent with the situation depicted. The control condition was a neutral statement of the certain type.	fMRI 1.5T block $p < 0.001$ (uncorrected)	SCZ (15) No mean results were presented, but no statistical difference was found between groups for age, gender and education level. SCZ group had lower IQ than HC PANSS pos. 13.1; neg. 17.1 Chlorpromazine-equivalent dose (mg/day): 410 ± 209.3	HC (16)
8. Lee et al. (2010) / TOM and EMP	View a cartoon story and predict what will happen based on characters' intentions (no false belief), their emotions or the social context, which includes counterintuitive reactions by the protagonists. In the control condition, the cartoon story was based on physical causality.	fMRI 1.5T block $p < 0.001$ (uncorrected)	SCZ (15) 26/15.1/Verbal IQ 11.4/ 13.1, 15.4 Illness duration (years): 4.6 ± 3.4 Chlorpromazine-equivalent dose (mg/day): 422.1 ± 23.7	HC (18) 25.8/15.4/ Verbal IQ 12.7
9. Mier et al. (2010) / EMP	Read a written statement conveying trait diagnostic information about persons (describing intention, emotion or physical characteristic),	fMRI 1.5 T event-related	SCZ (16) 34.25/11.44/114.31/NA	HC (16) 37/10.88/118

	then view a photo of the persons' faces with an emotional expression (anger, fear, happiness, neutral). Participants had to evaluate the congruence between the statement and the associated face.	$p < 0.001$ (uncorrected)	Mean SAPS score 1.5 Mean SANS score 7.94 Chlorpromazine-equivalent dose (mg/day): 901.59 ± 647.1	
10. Park et al. (2011) / TOM	Watch a short video with 2 protagonists in a social interaction who do or do not refer to the observer. Control condition consisted in observation of protagonists who are not conversing (e.g., 2 women sitting back to back).	fMRI 1.5T Block $p < 0.001$ (uncorrected)	SCZ (15) 29.5/ 13.6/ 98.9/ 19.8; 13.6 Paranoia scale: 48.9 Illness duration (years): 4.4 ± 3.4	HC (14) 28.2/ 15.1/ 106.7 37.9
11. Brüne et al. (2011) / TOM	Same as Brüne et al. (2008).	fMRI 1.5T Block $p < 0.05$ (uncorrected)	SCZ (22) 26.8/NA/NA/12.1; 14.5 Chlorpromazine-equivalent dose (mg/day): 112 ± 230 Illness duration (years): 3.3 ± 3.7	HC (26) 28.8/NA/NA
12. Das et al. (2011) / TOM	Watch a video animation of 2 triangles in an interaction that mimics cooperation or mocking. The control condition was a video animation of 2 randomly moving triangles. The participants had to respond concerning contingency (is there an interaction?).	fMRI 3T Block $p < 0.05$ (FDR)	SCZ (20) 34.5/11.09/NA/10.1; 18.2 Illness duration (years): 9.4 ± 6.5	HC (19) 33.5/16.4/ NA
13. Lee et al. (2013) / TOM	Read a short vignette involving a person holding a false belief and answer a question about his/her belief. The control condition was a false photograph vignette. The participant had to mention the outdated content in the false photograph vignette.	fMRI 3T event-related $p < 0.05$ (corrected)	SCZ (12) 38.3/12.5/NA/NA	HC (13) 42.5/ 14.2/NA

14. Pedersen et al. (2012) / TOM	Watch a video animation of 2 interacting triangles (smaller blue and bigger red). The participants had to indicate which action was depicted (select the word from several alternatives). Three types of triangle interaction were possible: TOM type with cooperation or mother and baby playing; non-TOM with one triangle chasing the other, and random movement as control.	fMRI 3T block $p < 0.05$ (FDR)	SCZ (15) 29/11.5/Verbal IQ 20.5/10.9; 14.9 Illness duration (years): 5.5 ± 6.3 Chlorpromazine-equivalent dose (mg/day): 629.6 ± 395	HC (14) 29.9/11.9/ Verbal IQ 21.3
15. Derntl et al. (2012) / EMP	Watch a static story of protagonists engaged in emotional interaction with one person's face masked. Participants had to choose the best matching emotional expression from two faces presented or, in the control condition, say if the masked face was left or right.	fMRI 3T event-related $p < 0.05$ (FWE)	SCZ (15) 34.2/NA/30.2 (MWT-B)/ 12.3; 14.6 Chlorpromazine-equivalent dose (mg/day): 329.9 ± 212.2 Illness duration (years): 7.3 ± 5.3	HC (15) 30.4/NA/32 (MWT-B)
16. Harvey et al. (2013) / EMP	Watch a short video vignette with persons describing autobiographical events with varying emotional expressions. Participants had to infer the protagonist's affective state and rate it during the video presentation on a Likert scale. In the control condition, participants had to rate how far to the left or right the protagonist's eyes were directed.	fMRI 3T block $p < 0.01$ (FDR, FWE)	SCZ (15) 42.4/12.7/NA/NA BPRS total score 40.1 BPRS positive 2.3 BPRS negative 1.9 SANS 27.1	HC (15) 42.9/14.1/NA
17. Varga et al. (2013) / TOM	Listen to stories depicting a social situation, first followed by an irony question and then by a comprehensive yes-no question. The control condition story depicted physical causality.	fMRI 3T event-related $p < 0.05$ (corrected)	SCZ (21) 37.95/13.43/106/13.81; 17 Illness duration (years): 11.95 ± 8.45	HC (24) 33.96/15.21/119.29

18. Eack et al. (2013) / TOM	Play a game with a human opponent where the participant had to pass the objects to the opponent and at the same time to take his/her perspective into account. In the control non-perspective task, participants were instructed to select an unambiguous item that was not occluded from the opponent's view.	fMRI 3T block $p < 0.05$ (uncorrected)	SCZ (9) and Schizoaffective disorder (11) 27.8/NA/97.9/NA Illness duration (years): 4.85 ± 3.18 Chlorpromazine-equivalent dose (mg/day): 308.05 ± 235.89	HC (20) 26.5/NA/106.55
19. Dodell-Feder et al. (2013) / TOM	Read a short vignette involving a person holding a false belief and answer a question about his/her belief. The control condition was a false photograph vignette. The participant had to mention the outdated content in the false photograph vignette related to physical state.	fMRI 3T event-related $p < 0.001$ (uncorrected)	SCZ (16) and Schizoaffective disorder (4) 38.8/15/108.7/3.1; 1.7	HC (18) 32.4/14.2/107.4
20. Hashimoto et al. (2014) / TOM	Watch a video animation of points depicting a biological movement (like walking) compared to random movement as a control. The participants had to identify the type of movement by a simple choice between two propositions.	fMRI 1.5T block $p < 0.05$ (FDR)	SCZ (17) 31.1/NA/NA/15.2/20.3 Illness duration (years): 7.1 ± 6.1 Chlorpromazine-equivalent dose (mg/day): 437.9 ± 356.5	HC (17) 27.7/NA/NA
21. Smith et al. (2015) / EMP	Same as Derntl et al. (2012).	fMRI event-related $p < 0.05$ (corrected)	SCZ (30) 33.6/NA/NA/SAPS 10; SANS 15.1 Illness duration (years): 13.6 ± 7.5 Chlorpromazine-equivalent dose (mg/day): 362.8 ± 237.7	HC (24) 34.4/NA/NA

22. Horan et al. (2014) / EMP	Participants had to observe and imitate facial expressions from the presented photos or execute a described emotional expression vs. a finger position in the control condition. Group comparisons of correlations between IRI summary index and observed face task were included in the meta-analysis.	fMRI 3T block $p < 0.05$ (FWE)	SCZ (23) 46.5/12.9/NA/NA BPRS total 33.7; positive 1.5; negative 1.7 Illness duration (years): 26.9 (mean) Chlorpromazine-equivalent dose (mg/day): 282.51 ± 162.49	HC (23) 46.7/14.9/NA
23. Ciaramidaro et al. (2015) / TOM	Same as Walter et al. (2009).	fMRI 3T event-related $p < 0.001$ (uncorrected)	SCZ (18) 14-32 years /NA/101.4/NA	HC (23) 15-27 years/ NA/106.8
24. Singh et al. (2015) / EMP	Look at photographs depicting misery, suffering and human loss with sadness content rated high by independent raters compared to mosaic photos as control condition.	fMRI 3T block $p < 0.05$ (FEW)	SCZ (14) 31.5/9.6/NA/ SAPS 8.6; SANS 12.6 Illness duration (years): 9.1 ± 6.3 Chlorpromazine-equivalent dose (mg/day): 389.3 ± 312.6	HC (14) 27.21/11.3/NA
25. Lee et al. (2016)/ TOM and EMP	Same as Lee et al. (2011) for false belief (verbal task). Emotion attribution: view IASP photos depicting emotions compared to photos without protagonists. Say if the protagonists felt positive, negative or neutral emotion (visual task).	fMRI 3T event-related $p < 0.05$ (corrected)	SCZ (15) 38.4/12.8/NA/NA	HC (14) 41.8/ 14.3/NA
26. Mier et al. (2016) / EMP	Same as Mier et al. (2010).	fMRI 3T event-related	SCZ (22) 38.05/10.36/97.23/14.32; NA	HC (22) 37.5/10.95/101.68

		$p < 0.005$ (uncorrected)	SANS 23.05 Chlorpromazine-equivalent dose (mg/day): 452.52 ± 176.02 Illness duration (years): 10.5 ± 6.84
27. Razafimandimby et al. (2016) / EMP	Listen to a short statement with emotional prosody depicting a social situation and identify the emotion (anger, happiness or sadness) compared to emotionally neutral statements where the participants had to identify the grammatical person of the protagonist (first, second or third person).	fMRI 3T event-related $p < 0.05$ (FWE)	SCZ (21) HC (25) 33.9/42.9*/NA/13.6;12 33.1/52*/NA Chlorpromazine-equivalent dose (mg/day): 340.3 ± 253 Illness duration (years): 11.9 (SD 7.9) * percentage of participants who achieved educational level superior or equal to the General Certificate of Educational A Level
28. Takano et al. (2016) / TOM and EMP	View a cartoon story showing protagonists in social interaction. Participants are asked to respond a question about the story involving false belief or social emotion. Control condition consisted in locating a specific object such as a ball in the story (present or absent).	fMRI 3T event-related $p < 0.001$ (uncorrected)	SCZ (16) HC (20) 25.5/NA/108.7/14.3; 17 24.7/NA/105 Chlorpromazine-equivalent dose (mg/day): 157.2 ± 218 Illness duration (years): 2.4 ± 4

TOM: Theory of Mind; EMP: Empathy; SCZ: Schizophrenia patients; HC: Healthy Controls; IQ: Intelligence Quotient; PANSS: Positive and Negative Syndrome Scale; N: Number; NA: Not Applicable; FDR: False Discovery Rate; FWE: Family-wise Error; fMRI: functional Magnetic Resonance Imaging; MWT-B: Multiple-choice Word Test; PET Scan: Positron Emission Tomography Scan; SAPS: Scale for Assessment of Positive Symptoms; SANS: Scale for Assessment of Negative Symptoms; BPRS: Brief Psychiatric Rating Scale; IRI: Interpersonal Reactivity Index

Table 2

Meta-analytic connectivity modeling (MACM) results for the conjunction analysis showing brain regions coactivated with the right IFG and left MTG.

Cluster (Volume mm ³)/ Brain region (Brodmann area)	MACM			
	x	y	z	z-Score
Cluster 1 (16552)				
left anterior middle occipital gyrus (BA37)	-44	-64	-6	0.10
Left posterior lobe cerebellum	-38	-56	-16	0.09
Left posterior middle temporal gyrus (BA37)	-50	-52	4	0.09
Left superior parietal lobule (BA7)	-30	-54	48	0.09
Left posterior middle temporal gyrus (BA39)	-46	-58	8	0.08
Left anterior middle temporal gyrus (BA22)	-54	-58	20	0.08
Left posterior superior temporal gyrus (BA39)	-50	-90	0	0.08
Left inferior occipital gyrus (BA19)	-38	-74	-8	0.07
Left inferior parietal lobule (BA40)	-46	-34	36	0.07
Left anterior superior temporal gyrus (BA22)	-56	-38	12	0.06
Left inferior frontal gyrus (BA9/44)	-46	6	28	0.05
Cluster 2 (7688)				
Left inferior frontal gyrus (BA9/44)	-46	6	28	0.08
Left anterior insula (BA13)	-38	20	6	0.07
Cluster 3 (5816)				
Right inferior frontal gyrus (BA9)	44	10	28	0.11

Right medial precentral gyrus, SMA	40	−6	46	0.07
Cluster 4 (5032)				
Right posterior middle temporal gyrus (BA37)	44	−62	−4	0.11
Right fusiform gyrus (BA 37)	40	−48	−14	0.10
Right posterior lobe cerebellum	44	−62	−4	0.07
Cluster 5 (3912)				
Left medial frontal gyrus, SMA (BA6)	−2	2	50	0.08
Cluster 6 (3744)				
Right superior parietal lobule, precuneus	30	−52	46	0.11
Cluster 7 (2872)				
Right anterior insula (BA13)	56	−38	18	0.07
Right anterior superior temporal gyrus (BA22)	50	−50	14	0.07
Cluster 8 (2768)				
Right claustrum	34	14	2	0.07
Right inferior frontal gyrus (BA46)	50	30	14	0.05
Cluster 9 (1992)				
Left precentral gyrus, SMA (BA6)	−32	−8	48	0.07
Cluster 10 (1776)				
Left amygdala	−22	−4	−10	0.11

Notes. x, y, z = peak voxel coordinates in Talairach space; Volume = volume of voxels in cluster obtained with MACM algorithm; IFG/MFG/SFG = inferior/middle/superior frontal gyrus; MTG = middle temporal gyrus; SMA = supplementary motor area.