

Abnormal Brain Activation During Theory of Mind Tasks in Schizophrenia: A Meta-Analysis

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Social cognition abilities are severely impaired in schizophrenia (SZ). The current meta-analysis used foci of 21 individual studies on functional abnormalities in the schizophrenic brain in order to identify regions that reveal convergent under- or over-activation during theory of mind (TOM) tasks. Studies were included in the analyses when contrasting tasks that require the processing of mental states with tasks which did not. Only studies that investigated patients with an ICD or DSM diagnosis were included. Quantitative voxel-based meta-analyses were done using Seed-based *d* Mapping software. Common TOM regions like medial-prefrontal cortex and temporo-parietal junction revealed abnormal activation in schizophrenic patients: Under-activation was identified in the medial prefrontal cortex, left orbito-frontal cortex, and in a small section of the left posterior temporo-parietal junction. Remarkably, robust over-activation was identified in a more dorsal, bilateral section of the temporo-parietal junction. Further abnormal activation was identified in medial occipito-parietal cortex, right premotor areas, left cingulate gyrus, and lingual gyrus. The findings of this study suggest that SZ patients simultaneously show over- and under-activation in TOM-related regions. Especially interesting, temporo-parietal junction reveals diverging activation patterns with an under-activating left posterior and an over-activating bilateral dorsal section. In conclusion, SZ patients show less specialized brain activation in regions linked to TOM and increased activation in attention-related networks suggesting compensatory effects.

Key words: fMRI/mentalizing/psychosis

Introduction

Poor social cognition is one of the defining characteristics of schizophrenia (SZ).^{1,2} A wealth of studies show that

schizophrenic patients are impaired in tasks that require mental state reasoning, perspective taking or an understanding of others' intentions and beliefs.^{3,4} These abilities are subsumed under the term theory of mind (TOM), which is defined as the ability to reason about mental states of others and to interpret and predict behavior based on an understanding of their minds.^{5,6}

Decreased TOM abilities are also evident in patients during remission,³ in relatives of schizophrenic patients and in individuals who bear a risk of developing a psychosis.^{7,8} Therefore, abnormal TOM is not a mere side effect of chronic SZ or an acute psychotic break but may rather be trait-dependent.^{3,9} Recent studies found that social cognition abilities like TOM are reliable predictors of global social functioning in schizophrenic patients.^{10,11} Furthermore, social cognition is able to explain a unique amount of variance in abnormal social functioning.^{12,13} Thus, although neurocognitive measures can account for up to 60% of variance in functional outcome,¹⁴ TOM is a strong additional factor to predict functional outcome in SZ.

In healthy participants, TOM tasks lead to activation in several brain areas like medial-prefrontal cortex (MPFC), superior temporal sulcus (STS), bilateral temporo-parietal junction (TPJ), and precuneus.¹⁵⁻¹⁷ Investigations on SZ patients are inconsistent and reveal decreased and increased activation of TOM-related regions. Several studies provide evidence for an increased activation in MPFC, left STS, left temporo-parietal junction, and precuneus cortex.¹⁸⁻²⁰ Other studies reveal decreased activation in similar regions²¹⁻²⁴ and some studies show increased as well as decreased activation in TOM-related brain regions.^{20,25} The diversity in neuroimaging findings is often discussed as being (at least partly) driven by the different tasks used to assess TOM processes and by heterogeneous patient groups.^{3,4,26} Heterogeneous findings

may also be due to the relatively small amount of participants in the individual studies. Therefore, meta-analytic studies are indispensable to gain an accurate insight in TOM abnormalities of SZ.

Sugranyes²⁷ provides a first meta-analytic overview of neuroimaging studies on TOM in SZ. Their findings indicate convergent under-activation for schizophrenic patients in the MPFC, middle temporal gyrus, posterior cingulate cortex, and the thalamus. Over-activation was identified in right parietal lobe and posterior cingulate cortex. Due to the lack of a sufficient amount of studies available at that time ($n = 9$), the range of possible analyses was limited. Meta-analyses on TOM in healthy controls commonly provide separate analyses for task subgroups¹⁶ since a pooled meta-analysis alone does not reveal possible task effects and therefore bears artificially increased variance. However, analyses of sub-tasks are difficult in samples where the number of available studies is limited, since a division in several smaller groups diminishes the power even more. Furthermore, the number of included studies per se is relatively small and a greater amount of data would lead to more reliable results.

Since the last meta-analysis,²⁷ more than 10 neuroimaging articles (meeting the criteria for Seed-based d Mapping meta-analyses) on TOM in SZ were published, thus providing an enlarged data pool which clearly enhances the statistical power. Furthermore, Molenberghs et al²⁶ put forward an alternative way of separating TOM tasks by means of 3 bivariate TOM task parameters: instructional focus (implicit vs. explicit), inference type (cognitive vs. affective), and modality of presentation (verbal vs. visual). Our meta-analysis aims to estimate a composite effect size of 21 individual studies assessing brain activation differences in TOM tasks between schizophrenic patients and control groups. Analyses of task subgroups (modeled after Molenberghs et al²⁶) are provided.

Heterogeneous patient samples represent a significant challenge for a unified interpretation of meta-analytic findings.^{3,4} We consider illness-specific parameters like the duration of illness and the severity of positive and negative symptoms as possible regressors in analyses which are provided in the supplementary material. Meta-analytic calculations are done using Seed-based d Mapping,²⁸ which was successfully used in meta-analyses on patient samples like obsessive-compulsive disorder²⁹ and autism.³⁰

Materials and Methods

Included Studies and Characteristics

To identify appropriate studies, we performed several MEDLINE searches using the keywords “schizophrenia,” “psychosis,” “theory of mind,” “mentalizing,” “perspective taking,” “fMRI,” “functional magnetic resonance imaging,” “PET,” “positron emission tomography,”

and “neuroimaging.” Criteria for the selection of relevant fMRI and PET studies were as follows:

- Studies included patients with a diagnosis of SZ (according to DSM or ICD criteria).
- Whole brain group comparisons (SZ vs. healthy controls) were reported in a standard stereotactic space (MNI or Talairach).
- All activation patterns clearly referred to TOM processes. We merely included studies that contrasted tasks requiring the processing of mental states with tasks which did not (eg, studies that contrast *false belief* vs. *false photo* conditions). If several contrasts were reported in a study, we selected the one that matched best the contrasts of the other studies. To avoid biases toward certain brain regions, only studies that used the same threshold throughout the brain (*within* their study) were included in the analysis. The thresholds do not need to be the same *between* all 21 included studies.

On this basis, 21 studies with a total of 623 participants (308 schizophrenic patients, 315 healthy controls) and 133 activation foci were included in the meta-analysis. The demographic and clinical characteristics of the participants are shown in table 1. Tasks descriptions of the individual studies are provided in supplementary figure SUP1.

Meta-Analytic Method

The current voxel-based meta-analysis was conducted using Seed-based d Mapping (SDM; formerly Signed Differential Mapping) software (<http://www.sdmproject.com>) version 4.31.^{28,29,44,45} Based on given foci of under- and over-activation, their respective statistical values and the sample size, SDM recreates maps of effect-sizes (Hedge's d) for each included study. The meta-analytic maps were thresholded using the recommended voxel-level (height) threshold of $P < .005$ (uncorrected) and a cluster-level (extent) threshold of 10 voxels, which is found to be an approximate equivalent to a corrected threshold of $P < .05$ in original neuroimaging studies.²⁸

Systematic whole-brain voxel-based jackknife sensitivity analysis was used to evaluate the replicability of the meta-analytic findings.

Comparisons of subgroups and meta-regressions were conducted using the built-in function of SDM. The reported findings were thresholded at values recommended for group comparisons ($P < .005$ (uncorrected), cluster-extent threshold: 10 voxels) and regressions ($P < .0005$ (Recommendation taken from AES-SDM tutorial from Joaquim Radua (Version May 2015), which can be retrieved from <http://www.sdmproject.com/software/tutorial.pdf>) (uncorrected), cluster-extent threshold: 10 voxels).

Separate meta-analyses for patients and healthy controls are provided in the supplementary material. Details

Table 1. Clinical Description of Patients With Schizophrenia Included in Theory of Mind Studies

Reference	Mean Age (SD) Patients/Controls	Gender M/F Patients; M/F Controls	Symptom Scales Mean Scores (SD)	Diagnosis/Recruitment/ Illness Duration (SD)	Medication Dose (mg): Mean (SD)
Brüne et al ¹⁹	27.9 (6.6)/26.5 (5.3)	3/6; 4/9	PANSS + 16.67 (5.7); PANSS – 15.67 (8.8)	First episode (<i>n</i> = 3); duration: 3 (4.23)	NLP: 244.44 (173)
Walter et al ²³	29.5 (6.0)/24.7 (2.6)	6/6; 6/6	PANSS + 17.75 (5.0); PANSS – 19.41 (3.9)	Inpatients; duration: 6.3 (5.2)	N/A
Benedetti et al ²⁵	37.2 (10.23)/35.1 (9.95)	14/10; 7/13	PANSS + 16 (4.58); PANSS – 21.66 (5.42)	Stable outpatients; first episode (<i>n</i> = 3); duration: 12.7 (6.96)	Clozapine <i>n</i> = 9; Risperidone <i>n</i> = 1; Aripiprazole <i>n</i> = 2; Haloperidol <i>n</i> = 2 NLP: 422.1 (237)
Lee et al ³¹	26 (4.3)/25.8 (2.2)	7/8; 9/9	PANSS + 13.1 (5.1); PANSS – 15.4 (4.1)	Stable outpatients; inpatients; duration: 4.6 (3.4)	N/A
Lee et al ²⁴	38.3 (10.7)/42.5 (7.7)	10/2; 10/3	N/A	DSM-IV (SCID-P); stable outpatients	N/A
Pedersen et al ¹⁸	29 (8.2)/29.9 (8.8)	9/6; 9/5	PANSS + 10.9 (2.8); PANSS – 14.9 (5.4)	Stable outpatients; duration: 5.5 (6.3)	NLP: 629.6 (395)
Eack et al ³²	27.8 (6.61)/26.50 (5.82)	14/6; 13/7	N/A	DSM-IV; stable outpatients; duration: 4.85 (3.18)	NLP: 308.08 (235.89)
Varga et al ³³	37.95 (9.06)/33.96 (8.51)	9/12; 10/14	PANSS + 13.81 (3.2); PANSS – 17.00 (5.4)	DSM-IV; remission; duration: 11.95 (8.45)	Amisulpiride <i>n</i> = 1; Aripiprazole <i>n</i> = 1; clozapine <i>n</i> = 4; Olanzapine <i>n</i> = 2; Quetiapine <i>n</i> = 2; Risperidone <i>n</i> = 2; Sertindole <i>n</i> = 1; Ziprazidone <i>n</i> = 1; Flupentixol <i>n</i> = 3; Haloperidol <i>n</i> = 1; NPL: 210 (142)
Harvey et al ³⁴	42.4 (11.8)/42.9 (8.6)	13/2; 13/2	SANS 27.1 (9.7)	DSM-IV (SCID-P); psychiatrically stable	N/A
Bedford et al ³⁵	39 (11)/31 (9)	7/4; 3/5	N/A	DSM-IV-TR; inpatients = 4, outpatients = 7; remission; duration: 12 (8)	Anti-psychotic medication
Rapp et al ³⁶	28.1 (N/A)/32.9 (N/A)	0/15	PANSS + 17.4 (N/A); PANSS – 16.00 (N/A)	DSM-IV; inpatients; clinically stable	NPL: 516.0 (237)
Russell et al ³⁷	36 (9)/	5/0; 7/0	N/A	DSM-IV; inpatients = 4, outpatients = 7; duration: 13 (7)	N/A
Brüne et al ³⁸	6.8 (5.5)/8.8 (4.1)	15/7; 16/9	PANSS + 18.2 (4.8); PANSS – 21.2 (7.1)	DSM-IV; inpatients; duration: 3.3 (3.7)	NPL: 475 (429)
Brunet et al ²¹	31 (6.5)/23.3 (1.68)	7/0; 8/0	N/A	DSM-IV; outpatients	Loxapine <i>n</i> = 1; Oxazepam <i>n</i> = 1; Tropatenine <i>n</i> = 2; Olanzapine <i>n</i> = 3; Haloperidol <i>n</i> = 2; Diprotacine <i>n</i> = 1; Tropatepine <i>n</i> = 1; Risperidone <i>n</i> = 2; Paroxetine <i>n</i> = 1; Citalopram <i>n</i> = 1 NPL: 901.59 (647.1)
Mier et al ³⁹	34.25 (6.95)/37.0 (8.18)	11/5; 11/5	SAPS 1.5 (1.37); SANS 7.94 (2.86)	DSM-IV; outpatients	N/A
Andreasen et al ²⁰	32.5 (11.0)/26.5 (6.4)	14/4; 6/7	SAPS 2.8 (N/A); SANS 2.1 (N/A)	DSM-IV; outpatients; duration: 8.96 (9.3)	No medication
Ciaramidaro et al ⁴⁰	range: 14–32/ range: 15–27	14/4; 19/4	N/A	DSM-IV; inpatients; duration: 6.25 (3.5)	N/A

Table 1. Continued

Reference	Mean Age (SD) Patients/Controls	Gender M/F Patients; M/F Controls	Symptom Scales Mean Scores (SD)	Diagnosis/Recruitment/ Illness Duration (SD)	Medication Dose (mg): Mean (SD)
Das et al ²²	34.5 (8.4)/33.5 (8.4)	20/0; 19/0	PANSS + 10.1 (3.0); PANSS - 18.2 (5.2)	DSM-IV; duration: 9.4 (6.5)	Lithium $n = 4$; Sertraline $n = 9$; 12 were on antipsychotic medications. NPL: 501.6 (402.8)
Dodell et al ⁴¹	38.8 (9.7)/32.4 (12.1)	12/8; 12/6	SAPS 3.1 (N/A); SANS 1.7 (N/A)	DSM-IV; inpatients; duration: 17.1 (12.2)	N/A
Pauly et al ⁴²	36.23 (9.46)/34.46 (8.58)	7/6; 7/6	SAPS 4.3 (N/A); SANS 7.0 (N/A)	DSM-IV; remission; duration: 12 (6.93)	N/A
Lee et al ⁴³	31.7 (7.3)/30.5 (8.8)	13/1; 13/1	SAPS 6.9 (2.6); SANS 7.6 (2.8)	DSM-IV; inpatients	NPL: 354.3 (N/A)

Note: Unless otherwise specified, neuroleptic dose (NPL) is expressed in chlorpromazine equivalents and duration of illness is reported in years. N/A, data not available; PANSS, Positive and Negative Symptom Scale; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

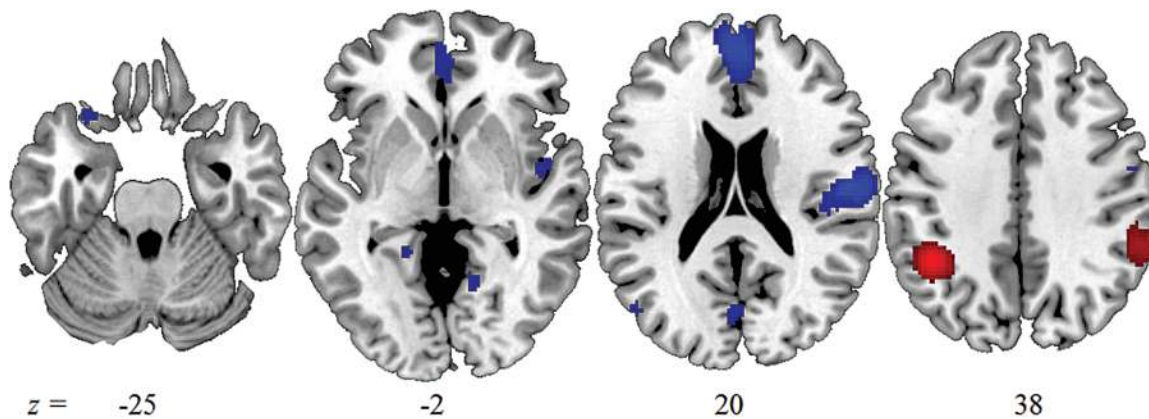


Fig. 1. Slices illustrate convergent under-activation (slices -25, -2, 20) and over-activation (slice 38) in patients compared to healthy controls at a voxel-level (height) threshold of $P < .005$ (uncorrected) and a cluster-level (extent) threshold of 10 voxels.

concerning methodological aspects are also shown in the supplements.

Results

Meta-Analysis

The pattern of abnormal neural activation in SZ compared to healthy controls is depicted in figure 1. The peak MNI coordinates, SDM Z-values, and cluster extent are listed in table 2.

The meta-analysis identified 9 clusters that revealed deviant brain activation for SZ patients. Convergent under-activation for patients was found in a widespread dorsal to ventral MPFC cluster, mostly located in the anterior rostral section of the medial frontal cortex.⁴⁶ Further under-activation was detected in a left orbito-frontal cluster. Right premotor cortex, medial occipito-parietal cortex, lingual gyrus, and the cingulate gyrus also revealed under-activation.

Our meta-analysis revealed convergent under-activation in a left lateral occipito-temporal cluster and convergent over-activation for patients compared to controls

in bilateral inferior parietal lobe (IPL). These clusters lie within a region which is often referred to as temporo-parietal junction.⁴⁷⁻⁴⁹ Left occipito-temporal and bilateral IPL are mapped against common TPJ atlases in supplementary figure SUP2.

Replicability of meta-analytic findings was tested by means of a jackknife sensitivity analysis. In sum, our data reveal strong robustness against changes in individual samples (lowest replicability in left orbito-frontal cluster in 14 out of 21 recalculations). We checked for publication bias by means of funnel plots and Egger test.⁵⁰ No evidence for publication bias could be found in the current dataset. Details concerning replicability and publication bias analyses are provided in the supplementary material.

Evaluation of Different TOM Tasks

To evaluate possible effects of different task types on the convergence of meta-analytic regions, the included studies were classified according to 3 criteria used by Molenberghs et al.²⁶ Therefore, each study was rated in the

Table 2. Results of the meta-analysis of functional brain abnormalities during theory of mind

Tasks in Schizophrenia						
Label	x	y	z	SDM-Z	Voxels	JK
<i>Under-activation</i>						
Medial prefrontal cortex	-2	52	18	1.612	1573	20/21
Frontal medial cortex	-4	40	-10			
Paracingulate gyrus	-2	42	-6			
R premotor cortex	54	-14	18	1.728	1101	21/21
Central opercular cortex	48	-6	4			
Postcentral gyrus	48	-10	28			
Precentral gyrus	56	-4	34			
Medial occipitoparietal	-4	-76	14	1.158	128	19/21
R lingual gyrus	12	-58	2	1.221	99	19/21
L orbito-frontal cortex	-30	22	-24	1.109	30	14/21
L lateral occipitotemporal	-48	-72	22	1.124	27	18/21
L cingulate gyrus	-18	-44	-2	1.084	24	18/21
<i>Over-activation</i>						
L inferior parietal cortex	-42	-48	38	-1.697	486	21/21
R inferior parietal cortex	58	-40	40	-1.114	405	19/21

Note: L, left; R, right; JK, jackknife analysis (number of subsamples that replicate the finding). Subclusters are reported for cluster sizes above 1000 voxels only.

categories cognitive (15 out of 21 studies)/affective (6/21), implicit (10/21)/explicit (11/21), and verbal (8/21)/visual (13/21). Classification details are listed in supplementary table 1. The reported findings describe the differences between patients and healthy controls for each subgroup (cognitive, affective, implicit, explicit, verbal, and visual) separately. Findings are illustrated in figure 2A1–C2. Note that the seemingly small overlap between our subgroup analyses and the main analysis depicted in table 3 is caused by the way we calculated the percentage of overlap (for details see supplementary material).

Replicability of General Meta-Analytic Findings in Task Subgroups

Table 3 indicates which of the clusters identified in the general meta-analysis could be replicated in the 6 task subgroup-analyses. Left inferior parietal over-activation was replicated in 5 subgroups but not for affective tasks. MPFC and right premotor cortex revealed robust under-activation in 4 out of 6 task subgroups. MPFC was not replicated for visual and implicit tasks, right premotor cortex was not replicated for affective and explicit tasks. Left orbito-frontal cortex and left cingulate gyrus show under-activation in 3 out of 6 subgroup analyses. Medial occipito-parietal, right lingual gyrus, and left lateral occipitotemporal show inconsistent replicability as they were replicated in merely 1 to 2 subgroups each.

Meta-Regressions

We calculated meta-regressions with the factors *duration of illness*, *positive symptoms*, and *negative symptoms*.

Although all meta-regressions revealed significant findings, visual inspection of the data showed that significant results were caused by several strong outliers in brain activation. Therefore, the meta-regressions are merely reported in the supplementary material and are not interpreted in the Discussion section.

Discussion

The aim of this meta-analysis was to investigate in which brain regions patients with SZ, compared to controls, show altered neuronal response during TOM tasks. Our main findings were (1) SZ patients show convergent under-activation in MPFC, left orbito-frontal cortex, right premotor cortex, and left lateral occipitotemporal cortex (posterior TPJ; TPJp); (2) patients reveal over-activation in a bilateral, dorsal section of the TPJ (TPJd); (3) aberrant activation in medial-prefrontal cortex, premotor cortex, and left TPJd was identified in most TOM task types whereas abnormal activation in the remaining cluster varied stronger with task type.

We meta-analyzed brain activation of 21 individual studies, which is far more than previous meta-analyses were able to include. A greater amount of data significantly increases the reliability of meta-analytic findings.⁵¹ The higher number of studies might also explain the diverging findings. To illustrate, although we replicate MPFC under-activation, we do not replicate activation patterns in other regions.²⁷

In line with previous research,²⁶ our task subgroup analyses showed that MPFC under-activation is robust against changes in task type whereas abnormal brain activation in other regions is identified only in several

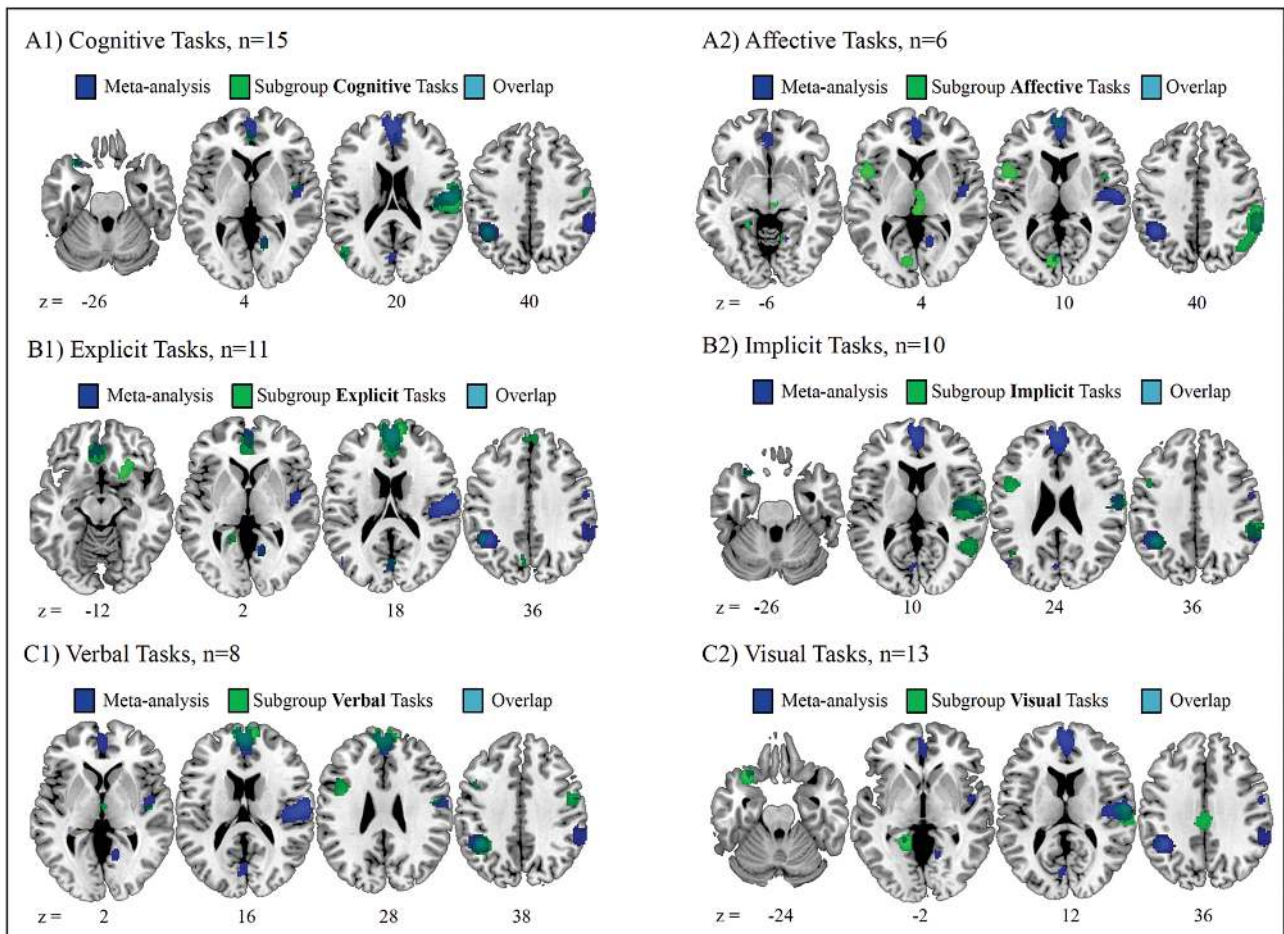


Fig. 2. Significant cluster revealed by the filtered subgroup analyses of the SDM group-comparison option. (A1-C2) To facilitate the comparison with the main meta-analysis, the results of the overall meta-analysis are indicated. Significant cluster (voxel level threshold $P < .005$, cluster extent = 10) of the subgroup analyses and the overlap between regions obtained from the subgroup analyses and the overall meta-analysis are shown as indicated by the color legend.

Table 3. Accordance Between Clusters of Subgroups With Main Meta-Analysis

Task Type	Medial Prefrontal Cortex	R Premotor Cortex	L Orbito-frontal Cortex	Medial Occipito-parietal	R Lingual Gyrus	L Lateral Occipito-temporal	L Cingulate Gyrus	L Inferior Parietal Cortex	R Inferior Parietal Cortex
Visual		22.9	10.8				2.3	32.0	
Verbal	20.5	11.5						21.9	
Cognitive	13.7	16.3	69.4		20.4	4.0		28.1	
Affective	25.4			8.1			1.6		5.5
Implicit		19.3	26.9					24.4	14.2
Explicit	15.0			8.0	18.6		7.4	22.1	
Σ	4/6	4/6	3/6	2/6	2/6	1/6	3/6	5/6	2/6

Note: Regions marked with a number revealed significant over-/under-activation in the respective subgroup at a threshold of $P < .005$, voxel extent 10. The specific number indicates to what extent (percent) the clusters of the task-specific analyses overlap with the clusters of the main analysis.

subgroups. This implies the following: (1) robust MPFC under-activation suggests a general dysfunction across TOM tasks in SZ; (2) aberrant activation in other regions could not be identified by previous meta-analyses due to the limited number of studies available at that time.

The Schizophrenic Social Brain

We showed under-activation in the schizophrenic brain during mentalizing in areas often subsumed under the term “social brain.”⁵² “Social brain” refers to the

neuronal processes related to social cue perception, experience sharing, inferring other people's thoughts/emotions and managing emotional reactions to others.⁵³ It includes activation in prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex, premotor cortex, and inferior parietal cortex.⁵⁴

Although great effort was made to disentangle the pathophysiology of TOM processes in SZ, our meta-analysis is the first to underpin a general dysfunction of the social brain network. The identified under-activation in these regions derives from decreased differences in brain activation between TOM and control tasks in SZ patients. Until now, this decreased difference between TOM and control task was either interpreted as hypo-mentalizing during TOM or hyper-mentalizing during control tasks.^{55,56} Accordingly, deficient social functioning is assumed to result from treating social agents like objects or the over-interpretation of social cues.^{40,57} Further research is urgently needed to expand our understanding of what over- and under-activation means with respect to over and under-mentalizing in SZ and how these effects are related to positive and negative symptoms of SZ.⁵⁸ Since the current meta-analysis analyzed the relative *contrast* between mentalizing and control tasks, it is beyond the scope of our analyses to foster one of these hypotheses. In neurophysiological terms, both assumptions result in a decreased difference in activation between TOM and control tasks. This implies that irrespective of whether hyper- or hypo-mentalizing causes the maladaptive performance, the schizophrenic brain differentiates less between TOM and control stimuli than a healthy brain. Regarding our finding of under-activation in SZ patients, we therefore propose the theory that the psychopathology of SZ is due to a less specialized social brain network. A decreased difference in brain response toward TOM stimuli versus control stimuli in SZ thus suggests a deficit in these brain regions to efficiently differentiate under which circumstances the processing of the social meaning of a stimulus is necessary. Such inefficiency might be the result of aberrant brain inter-connectivity⁵⁹ and decreased specialization is also found in language⁶⁰ and working memory⁶¹ studies in SZ.

In the current analyses, under-activation in regions of the social brain goes along with over-activation in bilateral dorsal TPJ. Our IPL and TPJp cluster correspond to dorsal and posterior TPJ components robustly identified in the literature⁶²⁻⁶⁶ (for overlapping maps see SUP2). Connectivity and independent component analyses emphasize functional differences between dorsal and posterior TPJ^{62,63}: TPJp is part of a fronto-parietal network⁶³ and is associated with social-cognitive processes⁶⁶ like mentalizing and the default mode network.⁶⁷⁻⁶⁹ Conversely, IPL (or also TPJd) is related to attention processes^{62,63} and general cognitive control.⁷⁰⁻⁷² Bilateral TPJd shows convergent over-activation in patients compared to healthy controls during mentalizing tasks. It is

possible that TPJd over-activation is associated with a compensatory response that recruits alternative strategies to foster task performance and might reflect the engagement of attention functions and cognitive control. However, these compensatory processes might fail (apparently SZ patients show disturbances in behavioral TOM tasks) for some reasons; First, it is not very likely that the computation applied by the attentional system is appropriate to the mental domain. Second, there is evidence that the attentional network and the regions where we identified under-activation inhibit each other⁷³ which led to the assumption that these networks reflect 2 incompatible modes that do not co-activate.

To date, there is no consensus concerning the pathophysiological mechanisms that cause aberrant neuronal response in SZ. Widespread abnormal activation, as identified in the current analysis, might be due to a general dysconnection in the schizophrenic brain.⁷⁴ SZ is associated with altered synaptic plasticity, which could modulate functional coupling⁷⁵ between cortical networks. This dysconnectivity approach is also capable of explaining a range of first rank symptoms in SZ.⁷⁶ Furthermore, drugs that affect synaptic plasticity have been shown to lead to psychotic symptoms in healthy subjects.^{77,78}

Implications for the Psychopathology of SZ

We showed that SZ patients revealed abnormal brain activity during various mentalizing tasks in a specific set of areas. In the following, we demonstrate how a deficient processing of social meaning is related to pathological outcomes in SZ. In healthy participants, activation in this set of areas is related to social cognition processes including social cue perception, experience sharing, the ability to infer other people's thoughts and emotions and to manage social reactions.⁵³

Social cue perception refers to the ability to read social cues from others and thus enables us to adequately respond in social interactions. Critically, patients with SZ show impairments in retrieving social cues from biological movements^{79,80} or faces.^{81,82} Neuroimaging studies show that these processes are related to activation in lingual gyrus⁸³ but also anterior cingulate, parietal lobe, and cuneus cortex.⁵³ This is in line with our finding of a decreased specialization for TOM stimuli in these regions, which in turn makes it difficult for patients to recognize relevant social meaning in the faces of others.

Experience sharing describes the phenomenon that the observation of another person's behavior leads to neural activation that normally becomes active when engaging in that behavior oneself.^{84,85} Such imitation processes are related to activation in premotor cortex which is robustly identified as being part of the mirror neuron system.⁸⁴⁻⁸⁶ It is assumed to play an important role in understanding the actions and intentions of others⁸⁷ as well as in imitation and empathy.^{88,89} A decreased differentiation

between TOM and control stimuli might make it difficult for patients to empathize or to learn about other's intentions and actions. In fact, there are studies highlighting problems with spontaneous mimicry and imitation.^{90,91} Impaired imitation abilities are also found in autistic patients⁹² and are assumed to determine an abnormal development of social and communicative functioning⁹³ in SZ.^{94,95} However, neurophysiological findings are mixed⁵³ and further research is needed to explore the link between deficient premotor cortex activation and imitation skills in SZ.

MPFC and TPJ are considered core components of the mentalizing system that co-activate during TOM tasks.^{96,97} These regions are associated with decoupling mechanisms, referring to the ability to dissociate between one agent's mental state from one's own beliefs and to differentiate between belief and reality.⁹⁸ We showed that the schizophrenic brain differentiates to a weaker extent between TOM tasks and control tasks in both, MPFC and TPJ. Less specialized brain response towards TOM stimuli might implicate a failure of de-coupling mechanisms in SZ. SZ patients therefore might be impaired at identifying the origin of beliefs, intentions, or action and have difficulties to dissociate them from reality. This might be a plausible explanation for delusory perception like paranoia and visual or auditory hallucinations. In fact, there is evidence that patients which tend to hallucinate have greater problems in attributing sources of spoken words.⁹⁹

Reacting in an adequate manner in social situations requires to (1) successfully identify socially relevant cues; (2) process the meaning of the observed cues; (3) evaluate on an appropriate social response. We already pointed out that SZ is characterized by impaired social cue perception. Processing the facial expression of another person requires the capacity to form complex representation of what others are thinking and to decouple them from own thoughts. Such meta-cognitive abilities are often associated with MPFC cortex,¹⁰⁰ which we showed is impaired in SZ. Behavioral symptoms of impaired meta-cognition are also evident in SZ^{101,102} and are known to be related to social and emotional withdrawal, awareness of illness, and quality of life.¹⁰² Choosing social behavior is associated with the personal valence of that situation. To illustrate, neuroimaging studies in learning and gambling tasks found that orbito-frontal cortex is involved in monitoring the reward value of stimuli and responses and therefore guides our behavior regarding the value of possible outcomes of that situation. Recent studies suggest impaired reward processing and motivational impairments in SZ.¹⁰³ Abnormal activation in orbito-frontal cortex could reflect difficulties in ascribing personal valence to people or social situations and a decreased social motivation to do so.¹⁰⁴ It is up to future studies to show how orbito-frontal dysfunction is exactly related to social response behavior in SZ. One way to do so would

be to assess brain response in SZ in a task where confederates could either give you helpful or unhelpful advices on how to get rewarded in a game.¹⁰⁵ If SZ patients have impairments in ascribing personal valence to others, their task performance (and most probably orbito-frontal brain activation) might differ from healthy controls.

Limitations

A disadvantage of a pooled meta-analysis is the high level of variance produced by combining diverging operationalization of TOM abilities. Since the results of a pooled analysis may obscure possible task effects we provide separate analysis of 6 task groups.²⁶ An additional limitation here is that the distribution is not the same for all task types. For the sake of clarification, we provide an overview of the task classification in the supplementary material.

Another limitation of the meta-analysis is that we were not able to assess the possible influence of medication on neural activation due to an insufficient amount of data. However, decreased neural response in TOM regions during TOM is also found in unaffected siblings of schizophrenic patients and in other relatives who bear an increased genetic risk to develop SZ.^{7,8} This minimizes the possibility that abnormal brain activation is the mere result of reiterating hospitalization and medication.

Furthermore, we were not able to draw a coherent conclusion about the influence of positive and negative symptoms on neural activation since regressions were carried by several outliers in brain activation estimates which tampered the results. Again, this must await future research in order to gain a sufficient amount of reliable data.

Conclusion

We identified under-activation in schizophrenic patients during TOM tasks in cortical regions normally specialized for social cognition. There was over-activation in attention-related regions which seems to be a failed attempt of the schizophrenic brain to fully compensate for malfunctions in the social domain. We propose that socio-cognitive deficits like an impaired TOM might be explained by less specialized social brain processes for which the brain is not able to compensate. It is now up to future studies to show how these findings can be embedded in targeted psychosocial treatments. We suggest 2 consecutive steps to do so; First, it is necessary to teach patients in which situations the extraction of social meaning is required to understand social situations. A possible way to train adequate processes could be to include training on basic TOM versus control stimuli in the therapy.

Second, current psychosocial treatments focused on affect perception and there are already studies showing its efficacy.^{106,107} A next step toward a better discrimination

of social cues in SZ would be to assess how trainings on experience sharing, mentalizing and social reactions would improve functional outcome in SZ. Patients could be trained via imitation exercises or role plays where patients learn how to interpret what others are thinking and how to adequately react in such situations.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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