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Social cognition in schizophrenia: Validation of an ecological fMRI task

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ABSTRACT

Neuroimaging studies have revealed brain regions involved in social cognition, which reportedly show functional alterations in schizophrenia. However, the social neural network has not been investigated with regards to language perception and social interactions in daily life. Here we developed and validated an integrative fMRI task to explore the neural basis of social cognition with regards to language perception in schizophrenia. The task comprised listening to film extracts and inferring mental states to characters. We first identified the functional network activated during the task in 28 healthy controls (HC). Next, we evaluated the reproducibility of Blood-Oxygen-Level Dependent (BOLD) variations in 14 HC participants. Finally, we investigated network impairment in 20 patients with schizophrenia (SZ) compared to HC. The HC group exhibited bilateral activation in the superior and middle temporal gyri (including the poles and the temporo-parietal junction). Overall, our novel integrative task induced activation of a functional network with good reproducibility and involved in language conveying social information. Compared to the HC group, the SZ group showed decreased recruitment of the right temporo-parietal junction. These findings may be useful for testing the impact of remediation on the brain, particularly on the network of language conveying social information.

1. Introduction

Social cognition comprises mental processes, such as theory of mind (ToM), emotion processing, and social perception, which subtend social interactions (Adolphs, 2010). Patients with schizophrenia show impairments of social cognition (Green et al., 2015; Lee et al., 2013; Pinkham et al., 2014; Savla et al., 2013), which are associated with low quality of life (Maat et al., 2012) and functional outcome (Fett et al., 2011). Recent neuroimaging studies highlight regions of the brain that are involved in social mental processes, and some investigations in patients with schizophrenia have detected functional and anatomical alterations of this network during social cognitive tasks. This network involves the medial prefrontal cortex (mPFC), temporo-parietal junction (TPJ), superior temporal sulcus (STS), temporal poles (TP), amygdala, insula, thalamus, and hippocampus (Bzdok et al., 2012; Fujiwara et al., 2015). Most prior neuroimaging studies involve basic tasks that focus on a single aspect of social cognition, and are generally based on visual stimuli. Few neuroimaging studies have considered language perception as a key component of social interaction, and none have examined language perception in a daily life situation (Fujiwara et al., 2015; Green et al., 2015). However, verbal language is a crucial and preferred method of social communication in humans (Fitch et al., 2010), with implicit and explicit processing of social cues, though it is rarely used in experimental paradigms, especially regarding schizophrenia (Brazo et al., 2014; Razafimandimby et al., 2016). Language disorders, such as thought disorders or auditory verbal hallucinations, are frequent in schizophrenia, and a large body of literature supports an impaired language network potentially related to decreased leftward hemispheric lateralization (Chou et al., 2017; Leroux et al., 2015).

In our present study, we developed and validated an integrative and innovative task to explore the neural basis of language conveying social information in patients with schizophrenia. The novel ecological task included movie excerpts showing verbal social interactions in a familiar daily context. First, in healthy control participants (HC), we tested the hypothesis that this ecological task would prompt neuronal activations matching both language and social brain networks described in the literature (content validity). We further assessed the functional neural network twice in a sub-sample of the HC group to examine the stability of task-induced neuronal activations (reproducibility or inner validity). Second, we investigated functional impairment in key regions of both

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Table 1
Demographic and clinical information of the sample.

	Retest-HC (HC-S2) $n = 14$	HC-S1 $n = 28$	SZ $n = 20$	*P* value
% Male	64.28	64.28	65	χ^2: 1
% Right handed	92.85	89.28	90	χ^2: 1
	Mean (standard deviation)			
Age in years	37.19 (7.23)	37.62 (8.47)	39.68 (8.08)	*t*-test: 0.40
Level of education[a]	12.71 (2.72)	13.42 (2.26)	12.35 (2.75)	*t*-test: 0.14
V-SIR	12.83 (2.57)	12.89 (2.55)	18.32 (5.64)	*t*-test: <0.01
Comprehension questionnaire	6.56 (0.51)	6.42 (0.74)	5.40 (1.27)	*W*-test: *<0.01*
Attribution questionnaire	3.41 (1.73)	3.27 (1.56)	4.04 (2.56)	*W*-test: = 0.24
Illness duration in years	/	/	16.38 (7.59)	/
PANSS Positive score	/	/	12.50 (5.31)	/
PANSS Negative score	/	/	11.80 (2.52)	/
PANSS General score	/	/	26.10 (5.46)	/
PANSS Total score	/	/	50.40 (10.18)	/
Chlorpromazine Equivalent (mg/day)	/	/	296.91 (167.63)	/

[a] Years after first grade student. HC, healthy controls; SZ, patients with schizophrenia.

language and social cognition networks in patients with schizophrenia (SZ) compared to HC (external validity).

2. Materials and methods

2.1. Participants

Content validity was tested in a group of 28 HC participants (HC-S1: the original sample) who performed the task in one fMRI session (Table 1). Of this group, 14 participants (HC-S2: the replication sample that underwent a second fMRI session) were also included in the reproducibility study, for which they participated in two fMRI sessions with an interval of five weeks. The study also included 20 SZ participants, who were matched with the 28 HC-S1 participants with regards to age, gender, handedness (Oldfield, 1971), and level of school education (Table 1). Inclusion criteria for all subjects were age between 18 and 65 years, written informed consent, no contraindication to MRI, no current pregnancy or breastfeeding, and no neurologic disorder. All subjects underwent evaluation with the Mini International Neuropsychiatric Interview (MINI), French Version 5.0.0. HC were free from any current or past psychotic disorders according to the MINI. Diagnoses were assessed by a fully qualified psychiatrist and met the Diagnostic and Statistical Manual of Mental Disorders criteria (DSM-IV-TR; American Psychiatric Association, 2000) for schizophrenia or schizo-affective disorders. Patients had to be stabilized without any change in their medication for at least the last 3 months.

This study was approved by a local ethical committee, and registered at www.clinicaltrials.gov (NCT02110017).

2.2. Language fMRI task

The experimental paradigm involved listening to five short excerpts of 50 s extracts from a French movie "Le premier jour du reste de ta vie" by Bezançon, in which five characters from the same family socially interacted with each other through usual language in daily life situations (condition INT). The chosen extracts conveyed common feelings or mental states through the context, prosody, and vocabulary used by the characters*. During the task, participants were asked to attentively listen to the social exchanges, focusing on the characters' conversations to understand their state of mind, e.g. their intentions, thoughts, and feelings. The reference task involved listening to excerpts of a Bollywood movie chosen for low affective tone and prosody in Hindi (condition HIN), a language unknown to all participants. During the reference task, the participants were instructed to "keep their eyes closed and to let their thoughts come and go". This reference task was chosen because it does not induce any implicit social cognitive process or any difference in activations between patients and healthy controls. Intelligible tasks, such as listening to language speech, induces reduced activation in the left language network (Dollfus et al., 2005; Koeda et al., 2006) and the mPFC (Dollfus et al., 2008) in patients with schizophrenia compared to healthy controls. The stimuli were presented in a block design over eight minutes, with alternating 50-second blocks in French or Hindi. Prior to the MRI scan, participants were given the instructions, and trained using a similar language task with different characters and context.

Immediately after the language scanning sessions, all participants were submitted to two in-house questionnaires each composed of seven questions to evaluate in the first questionnaire (the comprehension questionnaire), their understanding of the task and in the second (the attribution questionnaire) their social cognition performance during the test.

The comprehension questionnaire assesses general comprehension as well as some details of the listening story. Each question was scored 1 or 0 for an accurate or inaccurate / missing response, respectively. In the attribution questionnaire, subjects had to rate on a four range scale from totally disagree (value 0) to totally agree (value 3) their accordance to a question requiring emotional and mental state attributions in the social context. Each score was computed with the absolute value of the difference between the subject's value and the 28 HC mean value:

$$\Sigma\,|(\text{subject value}) - (\Sigma\ \text{healthy controls values})/28|$$

For example, if half of HC are totally disagree (value 0) and half are partially disagree (value 1) (mean value 0.5), and if a subject are totally disagree with the same question (value 0), then the question would be scored $0.5 = |0–0.5|$. The lower the difference, the more the answer to the question was considered as socially fair. The total attribution score is the sum of the subject scores of the seven questions. The attribution score, ranged from 1.8 to 13, 1.8 being the best score considered (see Table 1).

Moreover, quickly after scanning, task was assessed with two relevant mental state inferences with yes-no questions asked to the participant: 1/ Have you imagined the state of mind of the characters during the task? 2/ Have you put yourself in the actor's place to represent the mental state of the characters while listening?

2.3. Social cognition score

We used the Versailles-Situational Intentional Reading (V-SIR) quantitative assessment tool for investigating ToM deficits (attribution of intentions) in psychiatric populations (Bazin et al., 2009) (Table 1).

* The authors would be pleased to provide the audio files on request.

The V-SIR material consisted of six scenes from French movies lasting 10–70 s each. The scenes showed complex interactions between two or more persons involving hints, lies, and/or indirect speech. Each scene was followed by one question about the implicit intention of one of the characters. Five non-mutually exclusive interpretations were proposed to the subjects. The task was to independently rate the five interpretations as very unlikely, unlikely, likely, or very likely.

The V-SIR score was defined as the Manhattan distance between the patient's ratings and the mean ratings of the HC group (Bazin et al., 2009). For the computation of V-SIR scores, each probability rating was converted to a numerical value: 1 for very unlikely, 2 for unlikely, 3 for likely, and 4 for very likely. A single subject's total score was computed as the sum of the absolute values of the differences between the subject's ratings of each item and the mean ratings of healthy volunteers (Bazin et al., 2009).

The assessment duration was short (15–20 min) and was processed out of the scan.

2.4. Imaging parameters

For session 1, we used a 3-Tesla scanner (Intera Achieva 3T, Philips Medical System, the Netherlands) to acquire a T_1-weighted whole-brain anatomical image [3D-FFE-TFE sequence; matrix size, 256 × 256 with 180 contiguous slices; field of view (FOV), 256 mm; isotropic resolution, 1 mm; sagittal slice orientation; repetition time (TR), 20 ms; echo time (TE), 4.6 ms; flip angle (FA), 101°; inversion time (TI), 800 ms; SENSE factor, 2]. This was followed by acquisition of a T2-weighted functional scan (T2-TSE sequence; matrix size, 256 × 256 with 81 contiguous slices; FOV, 256 mm; isotropic resolution, 2 mm; sagittal slice orientation; TR, 5500 ms; TE, 80 ms; FA = 90°, SENSE factor, 2). To determine the T_2*-weighted functional volumes, we applied an echo-planar spin blood-oxygen-level dependent (EPI-BOLD) sequence (matrix size, 64 × 64 with 31 contiguous slices; FOV, 240 mm; isotropic resolution, 3.75 mm; axial slice orientation; TR, 2000 ms; TE, 35 ms; FA, 80°).

For session 2 among HC-S2 participants, we acquired a T_2-weighted functional scan and EPI-BOLD sequence to test the reproducibility. During this session, the other parameters were the same as described for session 1. The intersession interval was 34.71 ± 2.09 days.

2.5. Functional imaging processing

Data were preprocessed as previously described (Razafimandimby et al., 2007). We used Statistical Parametrical Mapping (SPM12; Wellcome Department of Cognitive Neurology, London, UK) to obtain anatomical and functional images in MNI space (Montreal Neurological Institute, Canada). The normalization parameters were chosen by default (Gaussian kernel, 8 mm). To achieve optimal coregistration of fMRI data from both sessions in the same stereotaxic space, the fMRI data were corrected for head motions and for differences in acquisition time between slices, and were coregistered with the anatomical T1 MRI data. Moreover, the anatomical MRI data were coregistered between sessions, and the coregistration parameters were applied to the fMRI data.

To perform the first level of statistical analysis, we applied the SPM12 regression model for computation of individual contrast maps (French *vs* Hindi: INT > HIN) and the corresponding *t*-maps. We modeled the expected Blood-Oxygen Level Dependent (BOLD) signal change using a boxcar function convolved with a standard hemodynamic response function (high-pass filter: 0.005 Hz). Motion parameters from the realignment procedure were entered into the model as covariates. Finally, we computed contrast maps (INT > HIN) for each subject and session.

2.6. Statistical analyses

2.6.1. Functional network involved during the task in HC-S1

To identify the functional network involved during the social cognition task, we entered the contrast maps for each HC participant from session 1 (HC-S1, $n = 28$) in a one-sample *t*-test, (SPM12), generating a mean functional map for the whole population. The significance threshold was set as $p < 0.05$, corrected by FWE at the voxel level and with a minimum cluster size of 20 voxels. Coordinates are reported in an automated anatomical labeling (AAL) atlas of the MNI MRI single-subject brain (Tzourio-Mazoyer et al., 2002).

2.6.2. Reproducibility of functional activation in HC

Analyses were performed following the seminal works of Maïza et al. (2010). The reproducibility of the activation in each participant was evaluated globally by the percentage of spatial overlap between the two sessions and locally by a voxel-wise computation of the between-session relative standard deviation (RSD). We subsequently used individual contrast maps and the corresponding *t*-maps from HC participants (HC-S2, $n = 14$) to evaluate local and global reproducibility.

2.6.2.1. Global reproducibility. We assessed global reproducibility (spatial distribution of activations) by computing the percentage of spatial overlap for each participant between sessions 1 and 2 (Maïza et al., 2011; Rombouts et al., 1997). To alleviate the bias of an arbitrary statistical threshold, the *t*-maps were thresholded at a constant activation volume (V1 = V2) set at 5000 voxels. The constant volume was set at 5000 voxels because, in both groups, it maximized the average percentage spatial overlap and represented the best compromise between the inclusion of irrelevant voxels at high activation volumes (false positives) and the exclusion of relevant voxels (false negatives) at low activation volumes (see Supplementary Fig. S1) (Maïza et al., 2010). We computed the average *t*-values of the 5000 most activated voxels of each individual *t*-map. To assess the stability across sessions of these average *t*-values, we used a Bland–Altman plot, a tool for assessing retest reliability from two measurements (Bland and Altman, 1999).

To display the global reproducibility, individual *t*-maps of the 5000 most activated voxels were binarized, and we computed probability maps of activations at each session. We further analyzed whether the percentage of spatial overlap was correlated with age, level of education, and intersession duration.

2.6.2.2. Local reproducibility. We also assessed local reproducibility on a voxel-wise basis. To this end, we computed individual relative standard deviation (RSD) maps from the contrast maps from sessions 1 and 2 (Maïza et al., 2011, 2010). This parameter corresponds to the absolute value expressed as a percentage of the ratio of the standard deviation to the mean. We computed RSD maps across sessions from the 2 contrast maps of each participant (session 1 and session 2). At each voxel, we computed the standard deviation (SD) between the 2 sessions, divided it by the absolute value of the average of the 2 sessions, and then multiplied this value by 100. Thus the formula is:

$$RSD = \left|\frac{SD}{Mean}\right| = \left|\frac{\sqrt{(x_1 - m)^2 + (x_2 - m)^2}}{m}\right|,$$

where m: average of percent signal change across session 1 and session 2; x1: percent signal change at session 1 and x2: percent signal change at session 2.

To avoid extremely large RSD values attributable to very small averages of the two sessions (Caceres et al., 2009), the maps were thresholded at an RSD value of 500% and we restricted this analysis to regions belonging to the network involved in this task (Aron et al., 2006; Whalley et al., 2009).

All voxel-wise statistical analyses were performed using SPM12. The significance threshold was set at $p < 0.001$, with a minimum cluster size of 20 voxels, without correction for multiple comparisons, unless otherwise specified. Other analyses were performed using R (http://cran.r-project.org).

2.6.3. Social cognition network in SZ compared to HC-S1

2.6.3.1. Behavioral data. Group differences in social cognition scores (V-SIR) were analyzed using a paired *t*-test. The effect size was calculated (Cohen's d) as follows. The mean V-SIR for patients was subtracted from the mean V-SIR for comparison subjects and divided by the pooled SD of both. Attention and performance were assessed through the comprehension and attribution questionnaires. Group differences in comprehension and attribution scores were analyzed using a Wilcoxon test. In addition, the tasks were tested using mental state inference questions with yes/no responses (cf. Section 2.2). Chi-square tests (χ^2) were performed to assess group differences in discrete variables.

2.6.3.2. Functional data. To analyze group differences in brain activations during the social cognition fMRI task, we performed second-level random-effects analyses with SPM12. Specifically, we employed a two-sample *t*-test to investigate differences between SZ and HC-S1, including the individual INT > HIN contrasts modeled at the first level. The significance threshold was set at $p < 0.001$, without correction for group differences and with a minimum cluster size of 20 voxels. The individual contrast maps were masked by the contrast map of all participants (inclusive, $p < 0.05$, FWE). The coordinates are reported in an AAL atlas of the MNI MRI single-subject brain (Tzourio-Mazoyer et al., 2002).

In order to take into account the mental state understanding and the comprehension process, individual contrast images of the contrast INT > HIN were correlated with the scores of attribution and comprehension questionnaire scores. To do that, the mean values of signal intensities for the INT > HIN contrast were extracted for each subject ($n = 48$) separately using REX (https://www.nitrc.org/projects/rex) via the contrast map of all participants (INT > HIN, $p < 0.05$, FWE) and then correlated with the attribution and comprehension scores using Pearson correlation analysis.

3. Results

3.1. Functional network involved during the task in HC-S1

Neural activations for the task effect were mainly detected during the intentional conditions (French story) as compared to the control condition (Hindi story) (INT > HIN) in the HC-S1 group ($n = 28$) (see Fig. 1 and Table 2). The most consistently activated voxels were located bilaterally in the superior and middle temporal gyri (including the poles and the TPJ defined as the posterior superior temporal sulcus and angular gyrus), the left supplementary motor area, the left precuneus, the right thalamus and caudate nucleus, the left inferior gyrus, the left precentral gyrus, the right and left hippocampi, and the cerebellum. We also detected small activations in the medial frontal cortex in few HC.

Table 2
Whole-brain analysis of the task effect ($p < 0.05$ FWE) for HC-S1.

Cluster (Region Label by AAL Atlas)	Side	Voxels	*t*-value	MNI coordinates x	y	z
Contrast Name: French story > Hindi story						
Cluster I	R	2326	14.59	32	−14	−18
Middle temporal gyrus						
Superior temporal gyrus						
Hippocampus						
Cluster II	L	3678	11.53	−30	−8	−22
Middle temporal gyrus						
Hippocampus						
Cluster III	L	69	9.96	−8	12	60
Supplementary motor area						
Cluster IV						
Cerebellar vermis (6)	L	128	9.48	−4	−74	−18
Cerebellum (VI)						
Cluster V	R	338	8.59	8	−44	−26
Cerebellar vermis (4, 5)						
Cluster VI	R	79	8.48	28	−56	−28
Cerebellum (VI)						
Cluster VII	L	67	8.14	−48	4	50
Precentral Gyrus						
Cluster VIII	L	81	8.10	−10	−46	40
Precuneus						
Cluster IX	R	32	7.64	14	−26	−2
Thalamus						
Cluster X	L	78	7.48	−44	20	22
Inferior frontal gyrus (*pars triangularis*)						
Cluster XI	R	179	7.33	12	0	16
Caudate nucleus						
Cluster XII	R	36	7.32	22	−74	−24
Cerebellum (VI)						
Cluster XIII	L	24	6.78	−26	−56	−28
Cerebellum (VI)						

HC: Healthy Controls; R: Right; L: Left; AAL: Automated Anatomical Labeling; MNI: Montreal Neurological Institute.

3.2. Reproducibility of functional activations in HC

3.2.1. Global reproducibility

In the Bland–Altman plot (see Supplementary Fig. S2) for the HC-S2 participants in both sessions ($n = 14$), the limits of agreement were from −4.25 to 6.03, and the mean difference was in mean ± SD 1.02 ± 2.69 (range, −4.21 to 5.28), showing that the threshold selection was reproducible. The HC-S2 group exhibited 63.51 ± 8.60% spatial overlap at the fixed volume of 5000 voxels (Supplementary Table S1). Fig. 2 illustrates the most consistently activated brain areas. Similar activation patterns were detected in both sessions. The activation reproducibility was greatest along the left superior temporal sulcus (STS), right anterior superior temporal sulcus, pars triangularis of the

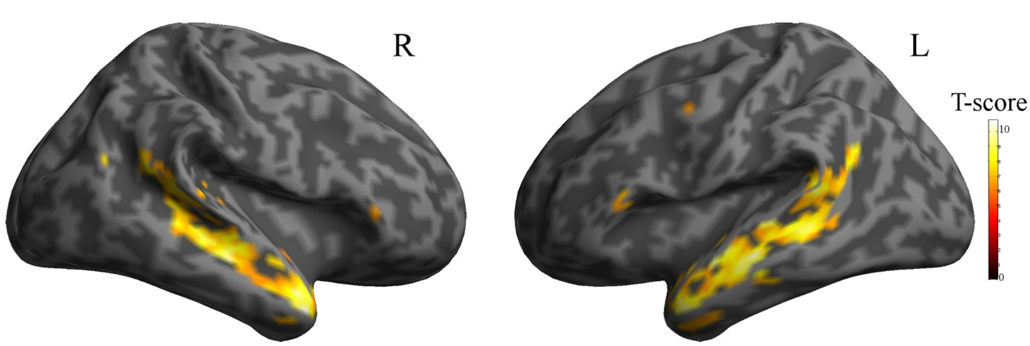

Fig. 1. Statistical mapping of T-scores of the task effect (INT > HIN) in healthy controls (HC-S1, $n = 28$). Contrast map was thresholded at $p < 0.05$, FWE, at the whole-brain level. Blood-Oxygen-Level Dependent (BOLD) variations are projected onto the Montreal Neurological Institute (MNI) single-subject brain template. Color bar indicates T-scores. L, left; R, right.

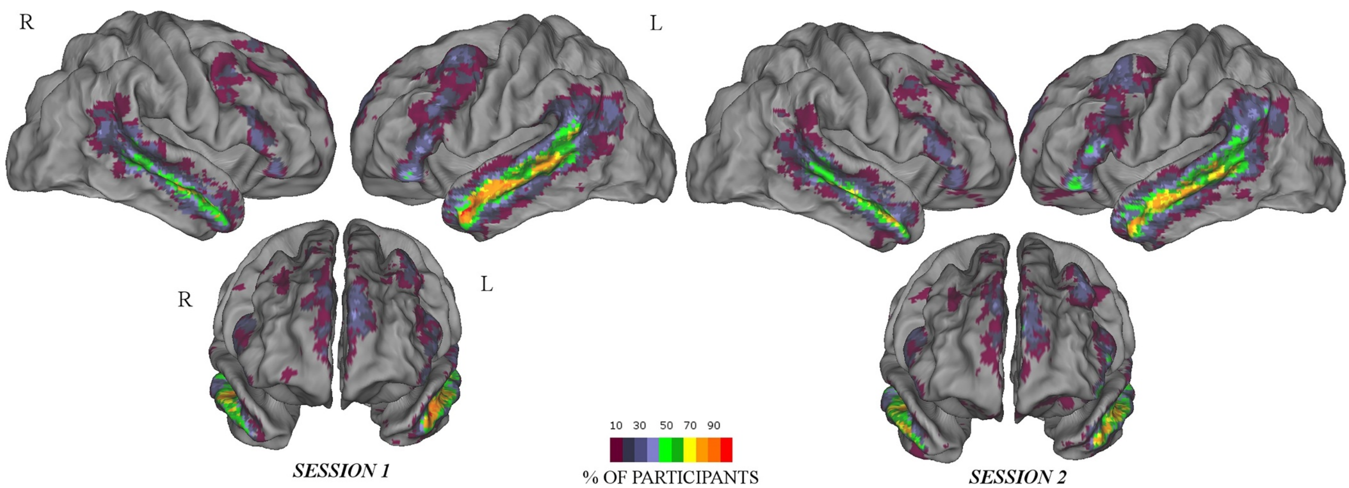

Fig. 2. Global reproducibility illustrated by activation probability maps from 14 healthy controls for sessions 1 and 2 (HC-S2). The color scale indicates the percentage of participants in whom each voxel was activated, among the 5000 most activated voxels. The maps are superimposed onto an inflated reconstruction of the Montreal Neurological Institute (MNI) template. L, left; R, right.

left inferior frontal gyrus (IFG), and only in few HC, the left medial frontal cortex. No factor significantly influenced activation reproducibility: age, $t(12) = -1.31$, $p = 0.21$; level of school education, $t(12) = 1.76$, $p = 0.10$; and intersession duration, $t(12) = 0.50$, $p = 0.62$).

3.2.2. Local reproducibility

Fig. 3 shows the local reproducibility patterns. The HC-S2 group showed high reproducibility (i.e. low RSD) in the temporal areas, particularly along the superior middle temporal sulci and the angular gyrus, but also in the IFG and the right anterior middle temporal gyrus.

3.3. Social cognition network in SZ compared to HC-S1

3.3.1. Behavioral data

The social cognition score (V-SIR) was in mean ± SD 12.89 ± 2.55 [range, 8.73 to 17.66] in HC-S1 ($n = 28$), and 18.32 ± 5.64 [range, 10.73 to 36.66] in SZ ($n = 20$). The between-group difference was significant (Cohen's $d = -1.31$; $t(24.59) = -4.01$, $p < 0.01$).

Controls performed significantly better on the comprehension questionnaire than the patients in session 1 (mean ± SD: 6.42 ± 0.74 in HC ($n = 28$), and 5.40 ± 1.27 in SZ ($n = 20$); W (28.16) = 3.24, $p < 0.01$). The attribution score was in mean ± SD 3.27 ± 1.56 and 4.04 ± 2.56 for HC and SZ, respectively. No significant session differences were identified (W (29.03) = −1.18, $p = 0.24$).

One hundred percent of the HC answered yes to the first mental state inference questions compared to 90% of the SZ. No between group differences were found (χ^2 (1) = 0.95, $p = 0.32$). A total of 57% of the HC answered yes to the second mental state inference questions compared to 30% of the SZ. No between group differences were found (χ^2 (1) = 2.45, $p = 0.12$).

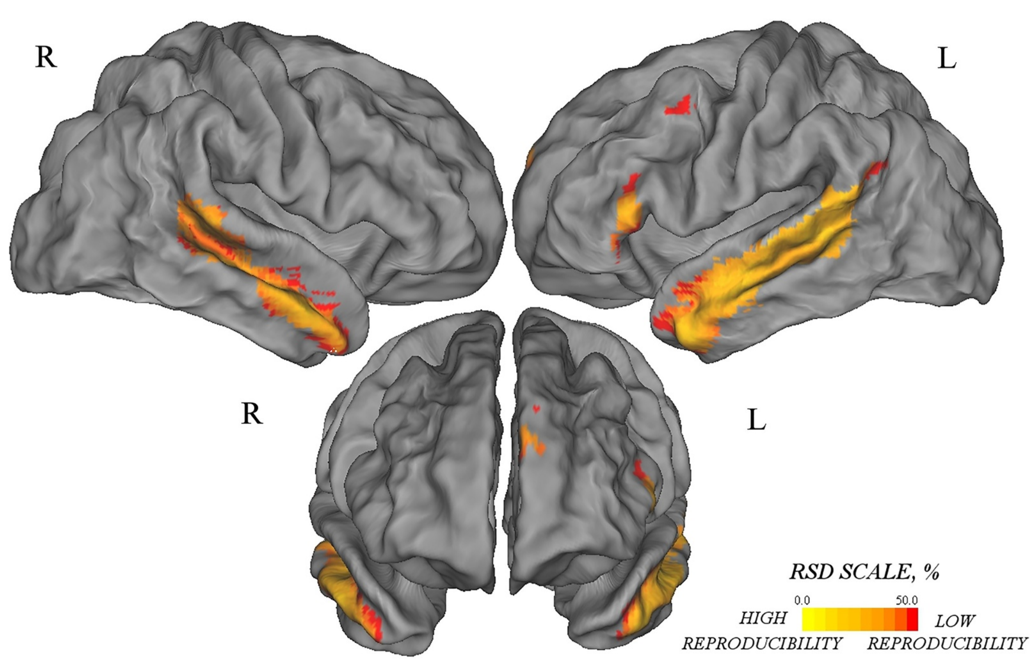

Fig. 3. Local reproducibility among the 14 healthy control participants (HC-S2). Average (within group) relative standard deviation (RSD) maps show local reproducibility of activations. Low RSD values correspond to high reproducibility. L, left; R, right.

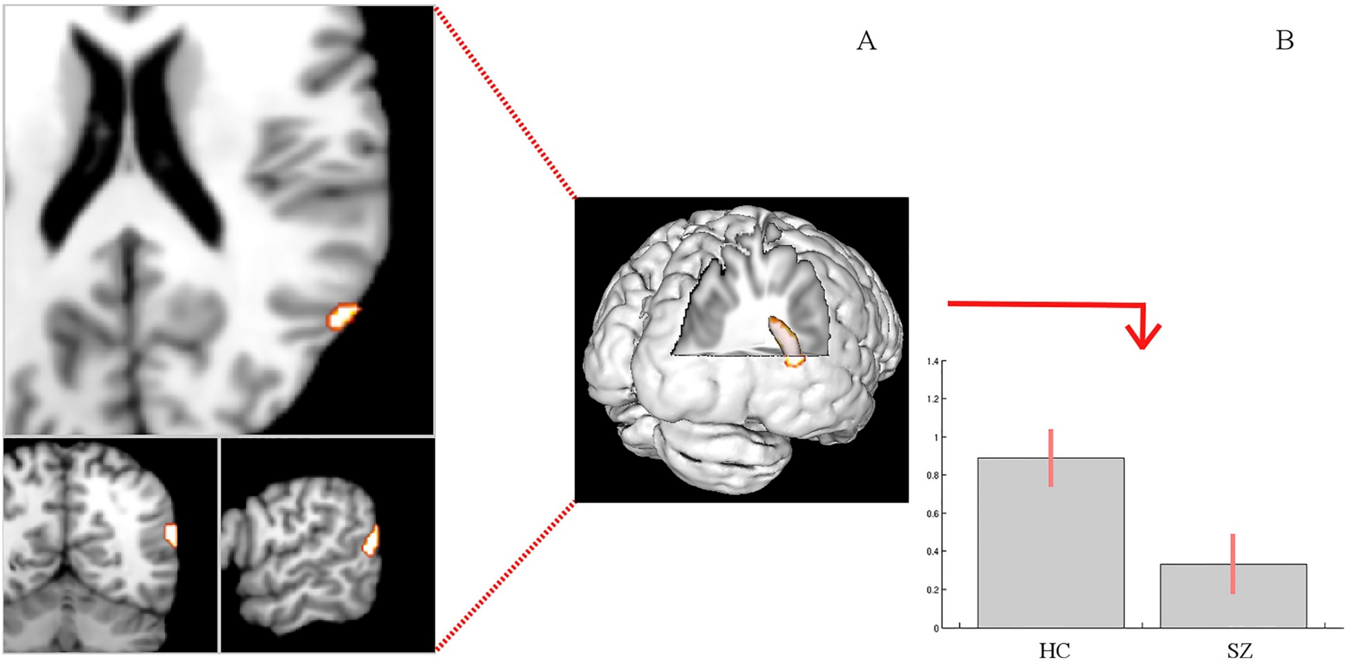

Fig. 4. Activation peak identified during BOLD comparison between healthy controls (HC-S1, $n = 28$) and patients with schizophrenia (SZ, $n = 20$). A) Blood-Oxygen-Level Dependent (BOLD) signal variations at the Montreal Neurological Institute (MNI) coordinates 56, −58, 18, corresponding to the right TPJ, which are superimposed onto a sagittal slice of an MNI single-subject template. B) Mean BOLD signal in the right TPJ in healthy controls (HC-S1, $n = 28$) and patients with schizophrenia (SZ, $n = 20$). Bar graphs plot the contrast estimates between the French story (intention) and the Hindi story (passive listening) ± standard error of mean in arbitrary units.

3.3.2. Functional data

The mean values of neural activity for the INT > HIN contrast correlated with the questionnaires scores revealed a significant correlation for the comprehension scores ($r = 0.38$, $p < 0.01$), but no correlation for the attribution scores ($r = -0.18$, $p = 0.20$).

Comparison between the two groups revealed lower BOLD responses in the right middle temporal gyrus in the SZ group compared to the HC group (see Fig. 4 and Table 3). In no region did we observe significantly higher BOLD responses in the SZ group than the HC-S1 group. No significant differences were found with FWE correction at the voxel level.

4. Discussion

This study is the first to use a language ecological fMRI task with language conveying social information in patients with schizophrenia. We found a high degree of both global and local reproducibility among healthy control participants, supporting the reliability of this task. Furthermore, a comparison of neural activations between the healthy control participants and patients with schizophrenia revealed that patients with schizophrenia showed decreased activation in the right temporal middle gyrus.

Table 3
Whole-brain analysis of the group effect ($p < 0.001$ uncorrected).

Region Label (AAL Atlas)	Voxels	*t*-value	MNI coordinates		
Contrast Name: French story > Hindi story HC-S1 > SZ			x	y	z
Right Middle Temporal Gyrus	47	4.5324	56	−58	18
Contrast Name: French story > Hindi story SZ > HC-S1			x	y	z
No significant differences					

HC, healthy controls; SZ, patients with schizophrenia; AAL, automated anatomical labeling; MNI, Montreal Neurological Institute.

4.1. Functional network involved during the task

The task predominantly induced activation bilaterally in the anterior and middle part of the superior and middle temporal gyri, which support auditory, phonological, and lexico-semantic processes (Vigneau et al., 2006). We also detected task-induced bilateral activation of the temporal and border of the inferior parietal areas with a leftward dominance, including the TPJ and the superior temporal sulcus. These activations match the neural bases of mentalizing processes, such as empathy (Farrow and Woodruff, 2007; Schnell et al., 2011) and ToM (Bzdok et al., 2016). Activation was also observed in the superior temporal gyrus (STG) and the IFG, which are brain regions associated with social cognition processes, such as perceiving social cues involving voice perception (Mazoyer et al., 1993). Thus, the task described in the present study mostly recruited brain areas involved in language and social interactions eliciting high-order inferential processes (Green et al., 2015). Overall, fMRI revealed bilateral activations in temporal, border of parietal, and frontal areas that overlap with the auditory, language, and social cognition brain network previously described in the literature (Binder and Desai, 2011; Van Overwalle and Baetens, 2009).

We also detected small activations in the medial frontal cortex. Brain regions such as the medial frontal cortex and the anterior cingulate cortex (ACC), which are associated with several aspects of social cognition, are also part of the default mode network (Eickhoff et al., 2016; Spreng et al., 2009). The default mode network might be also activated during the reference task (Hindi story), which could account for the underrepresentation of the medial frontal cortex in the present study.

4.2. Reproducibility of functional activations in HC

4.2.1. Global reproducibility

Validating our hypothesis, the activations induced by the ecological task were reproducible. The mean spatial overlap of 63.51%, which is in line with previous reports of spatial overlap ranging from 31% to 94% for sensory tasks (Gonzalez-Castillo and Talavage, 2011; Maïza et al., 2011) and from 35% to 50% for language tasks (Gonzalez-Castillo and Talavage, 2011; Maïza et al., 2010; Maldjian et al., 2002) among healthy control subjects. However, such comparisons must be interpreted cautiously, given the differences in methods and tasks among different studies. To our knowledge, only one prior study assessed global reproducibility in a social cognition task (Mohnke et al., 2013). Their results indicated good reliability of the brain activity evoked by a social cognition fMRI task paradigm; however, unlike our present study, their methodology involved intraclass correlation coefficients.

4.2.2. Local reproducibility

With regards to local reproducibility, the areas found to be involved in auditory and language processes were in line with the findings of a previous study (Maïza et al., 2011). The RSD maps of our present study showed bilateral values of between 15% and 40% in the STG, independent of age, level of school education, or intersession duration. To our knowledge, no prior study has assessed local reproducibility with a social cognition task. However, in a motor task, Marshall and colleagues found that left-hand versus right-hand and right-hand versus left-hand finger tapping induced 65% and 43% for activation amplitude, respectively, and that working memory induced an RSD of 34% for activation amplitude (Marshall et al., 2004). Tjandra also found a mean RSD of 20–30% between different days for a motor task (Tjandra et al., 2005). In addition, Yoo reported an RSD of approximately 30% in the Heschl's gyrus of healthy participants who were performing a passive auditory task (Yoo et al., 2007). These results are in accordance with the RSD maps of the present study.

4.3. . Social cognition network in SZ compared to HC

4.3.1. Behavioral data

We observed significant between-group differences in terms of social cognition score (*V-SIR*). Our results suggest that patients with schizophrenia had more impaired social cognition skills than healthy control participants, especially with regards to the attribution of intention (Bazin et al., 2009). However, participants sufficiently answered questionnaires positively without significant differences in the mental state inference questions (Table 1). This allowed us to consider that both SZ and HC participants were actively involved in the task during the scan, even if SZ patients demonstrated more difficulty in recalling factual items in the comprehension questions. Thus, despite attentional impairment, SZ patients were focused on social interactions and could answer questions about social cognition correctly.

4.3.2. Functional data

There were significant correlations between activations of the social cognition network and the comprehension scores but not with the attribution scores supporting the fact that the task was not a task involving only ToM process but rather a language task conveying social information.

Compared to healthy controls, patients with schizophrenia showed decreased activity in the right temporal middle gyrus, with a maximal cluster at 56, −58, 18 (x, y, z). This cluster location corresponds to the right TPJ, as described in the synthesis platform Neurosynth (http://neurosynth.org; (Yarkoni et al., 2011)), which is a region activated by social cognition processes. The significantly decreased neural activation in the rTPJ in SZ compared to HC likely reflects functional impairment in the social cognition brain network in schizophrenia. The rTPJ is a strongly connected area involved in high-level social process, such as perspective taking, empathy, (Hooker et al., 2010; Lombardo et al., 2010; Vogeley et al., 2004), ToM (Bzdok et al., 2012; Gallagher and Frith, 2003; Mars et al., 2012a; Saxe and Kanwisher, 2003; Van Overwalle and Baetens, 2009), and reorienting attention (Corbetta et al., 2008; Krall et al., 2015; Young et al., 2010). Indeed, patients with schizophrenia show impairment in these mental processes (Das et al., 2012; Green et al., 2015; Walter, 2009), as well as functional hypoactivation of the rTPJ during ToM tasks (Das et al., 2012; Dodell-Feder et al., 2014; Lee et al., 2011), highlighting the key role of the rTPJ during complex social interactions. However, other studies reported over-activation in the TPJ across different types of TOM tasks. A meta-analysis found, for example, over-activation, but in a more dorsal part of the TPJ (Kronbichler et al., 2017). When the maximal cluster of the present study (56, −58, 18 (x, y, z)) was mapped on common TPJ atlases (Igelström et al., 2015; Mars et al., 2012b), the location corresponded to the right posterior TPJ.

These results support the interest of using language tasks in investigations of social cognition rather than using visual stimuli, such as cartoons, which are less ecological and not as reflective of social interactions in real life.

The BOLD variation in the left TPJ did not differ between groups. Compared to its right counterpart, this area is less specific to mental attribution and could be related to general social cues involving representations of character actions rather than ToM (Vistoli, 2011). We also found no significant between-group differences in other areas involved in social cognition, such as the PFC or ACC (Bzdok et al., 2012; Fujiwara et al., 2015). These regions play key roles in social cognition (Adolphs, 1999; Frith, 2006) but findings in schizophrenia are inconsistent (Brüne et al., 2008; Green et al., 2015). Our present results might be explained by the activation of the PFC during the control task (Hindi). Indeed, this task comprised passive rest and mind-wandering, which elicit the default mode network (Mason et al., 2007; Raichle et al., 2001). Moreover, listening to verbal social interactions in an unknown foreign language—even though the instructions were to let the mind wander and not focus on the conversation—exposed the subject to the non-semantic emotional content of the sentences (prosody).

5. Limitations

The present study has several limitations. First, we did not test the reproducibility of fMRI activations in the SZ group due to the technical constraints of fMRI, and the difficulty of processing fMRI twice at a short interval in patients. Second, it would have been better to assess attention and performance during the scan, but our questionnaires were conducted after the scan considering that participants were actively involved in the task during the scan.

Third, the control task may have activated the default mode network (Mars et al., 2012a), potentially leading to undervaluing of activations in the medial PFC. It may be possible to use alternative control tasks, like reversed speech; however, this remains controversial (Brown et al., 2012). A control task based on the same language, with neutral interactions or monologues may succeed in better clearing the language network than a control task in a foreign language. However, it has been proved that patients with schizophrenia tend to overattribute mental states and some previous ToM tasks have shown overactivations in control task (Kronbichler et al., 2017). In the present study, the choice of the control task was done considering social cognition as a whole domain without focusing on only one process such as theory of mind. It is supported by the idea that even a neutral, emotionless speech may lead subjects to an implicit processing of social cues conveyed by language. Consequently, entanglement of language and social stimuli is part of the paradigm and was deliberately chosen to be considered as an ecological task.

Fourth, we did not have enough participants to reach large effect sizes with FWE correction. Thus, further studies with larger samples will be necessary to use this stringent corrected-threshold.

6. Summary and conclusions

In the present study, we propose an innovative and reproducible integrative task that involves language conveying social information, language and social cognition being two core communication features of the human species and impaired in schizophrenia. Our results highlight the entanglement of the bilateral temporal and parietal social networks involved during language, ToM and processing of social cues. Compared to healthy control participants, patients displayed hypoactivation in the rTPJ, in agreement with previous reports. The high test-retest reliability of fMRI activations indicates the stability of activations over time. This is a preliminary and essential condition to further test the impact of remediation on the brain, particularly on the network of language conveying social information.

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Contributors

Sonia Dollfus designed the study. Vincent Marzloff built the functional cognitive paradigm. Vincent Marzloff, Perrine Brazo and Sonia Dollfus recruited and evaluated the patients. Elise Leroux, Sonia Dollfus and Anick Razafimandimby managed the MRI sessions. Laurent Lecardeur managed the cognitive tests. Frederic Briend managed the literature searches and the analyses, wrote the first draft of the manuscript and undertook the statistical analysis. Pr. Sonia Dollfus revised the article and all the authors have approved the final manuscript.

Conflict of interest

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.03.004.

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