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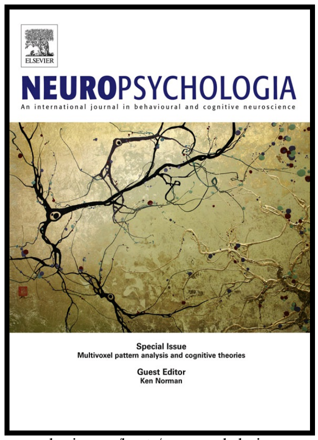

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Mentalizing in schizophrenia: a multivariate functional MRI study

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Abstract

Schizophrenia is associated with mentalizing deficits that impact on social functioning and quality of life. Recently, schizophrenia has been conceptualized as a disorder of neural connectivity. Network level analysis offers a means of understanding the underlying deficits leading to mentalizing difficulty. Using an established mentalizing task (The Triangles Task), functional magnetic resonance images (fMRI) were acquired from 19 patients with schizophrenia and 17 age- and sex-matched healthy controls (HCs). Participants were required to watch short animations of two triangles interacting with each other. The interactions could be perceived as either random (no interaction), physical (patterned movement), or mental (intentional movement). Task-based Partial Least Squares (PLS) was used to analyze activation differences and commonalities between the three conditions and the two groups. Seed-based PLS was used to assess functional connectivity with peaks identified in the task-based PLS. Behavioural PLS was then performed using the accuracy from the mental conditions. Patients with schizophrenia performed worse on the mentalizing condition compared to HCs. Task-based PLS revealed one significant latent variable (LV) that explained 42.9% of the variance in the task. This LV separated the mental condition from the physical and random conditions in patients with schizophrenia, but only the mental from physical in healthy controls. The mental animations were associated with increased activity in the inferior frontal gyri bilaterally, left superior temporal gyrus, right postcentral gyrus, and left caudate nucleus. The physical/random animations were associated with increased activity in the right medial frontal gyrus and left superior frontal gyrus. Seed-based PLS identified increased functional connectivity with the left inferior frontal gyrus (liFG) and caudate nucleus in patients with schizophrenia, during the mental and physical interactions, with functional connectivity with the LiFG associated with increased performance on the mental animations. The results suggest that mentalizing deficits in schizophrenia may arise due to inefficient social brain networks.

Keywords

Partial Least Squares; schizophrenia; theory of mind; fMRI; functional connectivity; superior temporal gyrus; inferior frontal gyrus; mentalizing; caudate nucleus;

1.0 Introduction

Schizophrenia is associated with marked deficits on a wide range of cognitive measures, including those assessing social cognitive ability (Bilder, 2009; Gur, et al., 2007; Kalkstein, Hurford, & Gur, 2010; Nuechterlein, et al., 2004). Theory of mind (ToM), an aspect of social cognition, refers to the cognitive ability of inferring agency, intentions, and beliefs that oneself and others hold. Several converging lines of research have identified deficits in ToM in patients with schizophrenia (Brune, 2005; Harrington, Siegert, & McClure, 2005) and explored the underlying neural architecture of these deficits (Sugranyes, Kyriakopoulos, Corrigall, Taylor, & Frangou, 2011). While the relationship between ToM and other neurocognitive domains awaits full explanation (Carrington & Bailey, 2009), specific regional activation differences when performing ToM tasks (Adolphs, 2009), coupled with behavioural evidence for distinct cognitive processes (Mehta, et al., 2013), suggest an independent role for ToM in understanding the cognitive dysfunction observed in schizophrenia.

ToM is a broad concept that has been measured using a multitude of tasks. One aspect of ToM thought to be relatively free of other cognitive demands, is implicit ToM ability (Frith & Frith, 2008). ToM can be considered to consist of both automatic, inflexible, implicit responses and thoughtful, mentally demanding explicit processes. Implicit ToM or mentalizing has been measured primarily using tasks that require viewing animated objects and inferring intention (Uddin, Iacoboni, Lange, & Keenan, 2007). One such task is The Triangles Task (Castelli, Happe, Frith, & Frith, 2000) that requires participants to watch an animation consisting of two triangles interacting in one of three ways; random, physical, or mental. Patients with schizophrenia perform significantly worse than controls at selecting the appropriate label for the animation, with deficits also observed in labeling the emotional content of the animations (Russell, Reynaud, Herba, Morris, & Corcoran, 2006). A functional neuroimaging study identified regional activation differences in patients with schizophrenia while performing The Triangles Task, including the right superior temporal gyrus, temporoparietal junction, and bilateral inferior frontal gyri (Das, Lagopoulos, Coulston, Henderson, & Malhi, 2011). To date, the only multivariate approach has employed independent components analysis (ICA), which determines the intrinsic networks independent of task and then investigates differences between the conditions of interest on these predetermined networks. Using this approach, Das et al (2012) identified reduced activity in patients with schizophrenia during the ToM condition, in lateralized fronto-temporal and insula networks, in addition to reduced suppression of the default mode network and a medial frontal network across all conditions.

Although ICA represents an excellent approach to understanding intrinsic brain networks, Partial Least Squares (PLS) allows for the analysis of a network of regions constrained based on task requirements (McIntosh, Bookstein, Haxby, & Grady, 1996). This method allows for the assessment of neural commonalities and differences within experimental conditions and between groups. Several lines of research have proposed that the integration and segregation of neural circuits is a key component of efficient cognition (Fornito, Zalesky, & Breakspear, 2015; Sporns, Tononi, & Kotter, 2005), with evidence that disruption of this segregation and integration may lie behind the cognitive dysfunction associated with schizophrenia (Pettersson-Yeo, Allen, Benetti, McGuire, & Mechelli, 2011). As ToM is a complex higher order cognitive ability subserved by a dynamic network of inter-related regions (Adolphs, 2009; Das, Calhoun, et al., 2012; Mohnke, et al., 2015), this approach may further the identification of structure-function correlates in healthy and clinical groups such as schizophrenia. Previous studies have not incorporated all conditions of the Triangles Task into the fMRI analyses (Das, Calhoun, et al., 2012; Das, Lagopoulos, Coulston, Henderson, & Malhi, 2012). Although contrasting the mental condition with the random condition may provide hints at the social brain network important for mentalizing, a more nuanced analysis should include the physical (or goal-directed) condition, as this controls for patterned or complex interaction without a mental component. Previous studies may have omitted this condition to simplify their analysis, but an approach like PLS allows for task complexity to be simplified within the analysis by reducing the data to latent variables able to explain the variance inherent in the data. Furthermore, PLS allows us to explore brain-behaviour relations; behavioural data has not previously been analyzed in parallel with imaging, this type of analysis has the potential to identify the underlying aberrant neural connectivity directly associated with mentalizing deficits in patients with schizophrenia.

In line with previous studies, we predicted that behavioural and neural differences would be identified between patients with schizophrenia and healthy controls. Specifically, we hypothesized that patients would perform worse on matching the intention-type with the animation, especially for the animations displaying mental interaction. Moreover, PLS analysis would identify neural commonalities between the three conditions, but crucially, would identify unique neural representations associated with mentalizing compared with the goal-directed or random interactions. Peaks associated with the mental condition will be further investigated using seed-based and behavioural PLS to investigate whole-brain functional connectivity differences with these regions in patients with schizophrenia and in association with accuracy on the mental condition.These differences were expected to be in key 'social brain' regions, such as the medial prefrontal cortex, inferior frontal gyri, temporoparietal junctions, and superior temporal gyri.

2.0 Methods

2.1 Participants

Nineteen patients with schizophrenia were recruited from the Queensland Centre for Mental Health Research (QCMHR). Individuals were comprehensively ascertained by trained clinicians using: (i) the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger, et al., 1994) (ii) Family Interview for Genetic Studies (FIGS) (Gershon, et al., 1988; Maxwell, 1992); (iii) information extracted from all available medical records; (iv) Narrative summary prepared by the interviewer and based on all information obtained from the DIGS, FIGS and medical records. The narrative summary was invaluable in recording the first-hand impressions of the interviewer. This facilitated diagnostic assessment by augmenting the DIGS interview information, especially when the participant's responses lacked clarity; (v) Best Estimate Final Diagnosis (BEFD) (Leckman, Sholomskas, Thompson, Belanger, & Weissman, 1982) was assigned by two experienced research psychiatrists independently reviewing all available information then conferring to assign a consensus diagnosis; one of us (BM) reviewed every case. Diagnostic inter-rater reliability was assessed using standard procedures (Suarez, et al., 2006). Age and sex matched HCs (N=17) were also recruited through QCMHR. The HCs had no history of psychiatric or neurologic illness.

2.2 Intelligence testing

Full-scale IQs were ascertained using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999), which comprised four subtests (Vocabulary, Similarities, Block Design, Matrix Reasoning). IQ assessments were carried out by a trained researcher (AM) and a trained psychiatric nurse, under the supervision of a clinical neuropsychologist (GR).

2.3 Behavioural Statistical Analysis

All analyses were carried out in SPSS version 20.0.0. Accuracy scores were calculated for each participant in each of the 3 conditions (out of 4) plus total correct (out of 12). Number of each interaction type selected was also compared between groups. A repeated measures Analysis of Variance (RM-ANOVA) was used to assess specific differences across conditions (random, physical, and mental) across the two groups (HCs and SZ). Independent samples t-tests were also used to assess differences between groups on the individual measures. Pearson's correlations were employed to investigate association between IQ and brain activation.

2.4 fMRI behavioural task and procedure

The Triangles Task (Castelli, et al., 2000) is a measure of mentalizing used in previous fMRI studies with patients with schizophrenia (Das, Calhoun, et al., 2012; Das, Lagopoulos, et al., 2012; Pedersen, et al., 2012). It involves viewing animations consisting of a large and small triangle interacting on a screen for a period of 36 seconds. Following each animation was a rest period of 15 seconds in which time the participant was prompted to make a judgment as to whether the interaction was a) random – no meaningful interaction b) physical – the actions or movements of one triangle are dependent on the other triangle or c) mental – the triangles interact in such a way that it appears that one triangle is trying to influence or manipulate the thoughts or emotions of the other triangle. Prior to the fMRI, all participants viewed one example of each condition to familiarize them to the task. Four videos per condition were presented, resulting in a total of 12 videos.

Participants completed the task while undergoing an MRI scan; the videos in the task were presented using E-Prime software (https://www.pstnet.com/eprime.cfm) on a computer screen that was seen by participants through a tilted mirror attached to the MRI head coil. Hemodynamic responses were recorded whilst participants watched the video with responses provided after the completion of each animation during a 15 second rest period. Responses were made using an MR-compatible button-press, participants were required to press the left button if physical, the right button if mental, or no response for random. As these responses were made during the rest period, they had no impact on the task-based analysis. The responses provided the behavioural measures of accuracy across the three conditions (random, physical, and mental) within the Triangles Task.

2.5 Neuroimaging acquisition

Neuroimaging was performed using a 3-T Siemens Magnetom TimTrio at the Centre for Advanced Imaging at the University of Queensland. High-resolution T1-weighted, 192 slices were acquired with 0.9mm^3 resolution, with a TR= 1900ms, TE = 2.3ms, TI= 900ms. Acquisition time was 4 minutes and 26 seconds. A ten-minute echo-planar imaging (EPI) scan [33 axial slice, matrix = 64x64 in plane resolution, slice thickness = 3.0mm, 301 volumes (including 5 dummy scans), TR= 2100ms, TE= 32ms, FOV=230mm, voxel size = 3.6x3.6x3.0, flip angle= 90deg, slice gap= 10%, interleaved ascending axial slice acquisition] were acquired for each participant.

2.6 Task based PLS analysis

Preprocessing of the fMRI data was performed in Statistical Parametric Mapping Version 8 (SPM8) (www.fil.ion.ucl.ac.uk/spm) and consisted of motion correction, coregistration of the functional images to the structural image, segmented into grey matter, white-matter, and cerebro-spinal fluid, spatial normalization to standard MNI space, and spatial smoothing using an 8mm Gaussian kernel. All images were inspected for excessive movement, with all images deemed acceptable and included in the analysis. The smoothed preprocessed grey matter images were entered into a Partial Least Squares (PLS) (McIntosh, Chau, & Protzner, 2004) analysis performed on MATLAB 7.10.0 (R2010a). Data for the three conditions (mental, physical, & random) for the two groups (HCs & SZ) were included in a block design analysis. PLS is a multivariate method that assumes that brain function reflects the coordinated involvement of networks of brain regions rather than the independent activity of specific brain regions. PLS identifies the voxels that covary together across the conditions. It also allows all conditions to be analyzed simultaneously allowing for the identification of commonalities as well as differences. PLS produces latent variables (LVs), singular values with linear contrasts representing brain regions able to differentiate conditions within the experimental design. The significance for each LV was independently determined using a permutation test with 500 permutations (McIntosh, et al., 1996). The weights of each voxel contributing to the LVs are termed saliences. The reliability of the saliences for the brain voxels characterizing each pattern identified by the LVs was determined by a bootstrap estimation of the standard errors (McIntosh, et al., 2004). The salience of each voxel was multiplied by the signal of each brain voxel for each participant; these were then summed across the entire brain to give the individual 'brain scores' for a given LV. Peak voxels with a salience ratio >3 were considered reliable, as this approximates $p<0.005$ (Burianova & Grady, 2007; Sampson, Streissguth, Barr, & Bookstein, 1989). Only clusters exceeding 10 voxels and at a greater distance than 10mm from another cluster are reported here. Brain scores indicate the degree to which each participant expresses the pattern of activity identified by an LV across each condition. Following the task-based PLS, peaks associated with the mental interaction were further investigated using seed-based PLS.

2.7 Seed-based PLS connectivity analysis

Following the task-based PLS analysis, selected regions of interest (ROI) associated with the mental animations were investigated for functional connectivity patterns between conditions and groups. All peaks associated with the mental condition were initially screened for differences in functional connectivity patterns between conditions. The seed regions were defined by extracting the average response for each participant and condition using a neighbourhood of 1 voxel around the target voxel but only including the voxels that meet the bootstrapped threshold criteria from the task-based PLS. This results in a ROI (max 27 voxels) for which the MRI signal was extracted for each subject. This is then entered into the analysis to identify brain regions that covary with the signal from the ROI. In the identical process to task-PLS, the resulting correlation maps were analyzed with singular value decomposition to produce LVs. Again, the significance for each LV was independently determined using a permutation test with 500 permutations (McIntosh, et al., 1996). In addition, the reliability of the saliences for the brain voxels characterizing each pattern identified by the LVs was determined by a bootstrap estimation of the standard errors (McIntosh, et al., 2004). The salience of each voxel was multiplied by the signal of each brain voxel for each participant; these were then summed across the entire brain to give the individual 'brain scores' for a given LV. Peak voxels with a salience ratio >3 were considered reliable, as this approximates $p<0.005$ (Burianova & Grady, 2007; Sampson, et al., 1989). Only clusters exceeding 30 voxels and at a greater distance than 10mm from another cluster are reported here.

2.8 Behavioural PLS analyses

Finally, the accuracy scores from the mental condition were entered into behavioural PLS analyses with the task-based and seed-based functional connectivity data. In an identical procedure to the seed-based functional connectivity analysis, accuracy scores for the mental condition were entered into the analysis to identify brain activation or functional connectivity patterns that covaried with performance. As we were only interested in performance on the mental conditions the fMRI data from the physical and random conditions were removed prior to analysis.

2.9 Association with IQ

All LVs found to significantly differentiate HCs and SZ patients were correlated with IQ to determine any relationship.

3.0 Results

All groups were matched for age and sex; however, HCs scored higher on the WASI full scale IQ measure than the SZ group (see Table 1). Missing behavioural data across all conditions for one patient was due to either a fault in the equipment resulting in the failure to record responses or the subject failed to respond. As the activation data was also an outlier they were removed from the analysis resulting in a total sample of 18 SZ and 17 HC. All behavioural measures were normally distributed. Patients and controls did not differ on the number of each condition selected (see table 2.). However, compared to SZ patients, HCs were more accurate at identifying the interactions correctly (9.70 v 7.89, $p=0.01$). Although worse overall, the interaction between condition and group just failed to reach significance, $F(1, 33)=7.88$, $p=0.056$. Specifically, HCs were more accurate at identifying the mental interactions (3.24 v 2.17, $p<0.01$) (see Table 2).

Table 1. Demographic and full-scale IQ data across groups.

	HC (N=17)	SZ (N=19)	t/ χ^2	p-value	Cohen's d
FSIQ	115.06 (13.44)	96.47 (10.28)	4.69	<0.01	1.55
Age (years)	46.06 (10.40)	45.21 (9.82)	0.25	0.80	0.08
% Male	52.9	57.9	0.09	0.77	
Age at onset (yrs)	-	24.0 (5.69)	-	-	
Illness duration (yrs)	-	21.21 (8.05)	-	-	

Table 2. Behavioural scores for healthy controls and schizophrenia patients

	HCs (N=17)	SZ (N=18[#])	T	p-value	Cohen's d
Random Selected	3.65 (0.70)	3.89 (0.96)	-0.84	0.40	0.28
Physical Selected	4.18 (0.95)	4.39 (1.29)	-0.55	0.59	0.18
Mental Selected	4.18 (0.95)	3.72 (1.57)	1.03	0.31	0.35
Random Correct (out of 4)	3.53 (0.62)	3.33 (0.69)	0.88	0.38	0.30
Physical Correct (out of 4)	3.00 (1.06)	2.39 (1.09)	1.68	0.10	0.57
Mental Correct (out of 4)	3.24 (0.97)	2.17 (1.20)	2.89	<0.01	0.98
Total Correct (out of 12)	9.70 (1.84)	7.89 (2.03)	2.69	0.01	0.91

[#] data for one Sz patient not recorded due to technical failure

3.1 Task-based PLS results

The task-based PLS identified one significant LV ($p<0.008$), which explained 42.9% of the variance. This LV separated activation during mental from physical interactions in both SZ and HCs. The network associated with physical animations was also significantly associated with random animations in the SZ group only. Figure 1 displays the mean brain scores for this LV. As can be seen in Table 3, mental interactions involved clusters in the inferior frontal gyri bilaterally, left superior temporal sulcus, right precentral gyrus, and left caudate; physical and random interactions (physical only for HCs) involved clusters with peaks in the right medial frontal gyrus and left superior frontal gyrus(see figure 2). Although the second LV did not reach significance (p=0.09), it explained 31.7% of the variance and separated random from physical conditions. Random animations involved activation with a peak in the right superior temporal gyrus and physical animations were involved with activation in the right precentral gyrus, left medial frontal gyrus, left inferior parietal lobule, right postcentral gyrus (x2), right cingulate gyrus, and the left insula (see table 3).

Table 3. Regions activated during the viewing of the Triangles Task differentiated by the latent variable from task-based PLS analysis

	Peak region	MNI coordinates			Voxels	Ratio
		x	y	z		
LV1						
Mental						
	R Inf frontal gyrus	54	32	12	76	4.21
	L Inf frontal gyrus	-43	29	-3	27	3.54
	L Sup temporal gyrus	-65	-32	12	43	4.63
	R Postcentral gyrus	68	-14	22	47	4.17
	L Caudate nucleus	-4	11	0	49	3.90
Physical/Random						
	R Med frontal gyrus	14	25	48	47	3.78
	L Sup frontal gyrus	-22	44	-14	27	3.55
LV2						
Physical						
	R Precentral gyrus	61	0	33	66	4.90
	L Medial frontal gyrus	-7	43	-15	204	4.28
	L Inf parietal lobule	-40	-65	42	65	4.19
	R Postcentral gyrus	50	-14	15	145	3.98
	R Postcentral gyrus	65	-18	36	23	3.69
	R Cingulate gyrus	18	-43	24	83	3.92
	L Insula	-47	-22	21	132	3.65

Ratio = salience/SE ratio from bootstrap analysis

*** Figure 1 and 2 approx here ***

3.2 Seed-based functional connectivity results

Of the five peaks associated with the mental animations, two revealed patterns of functional connectivity that differed between groups or conditions. One further SZ patient was removed from the functional connectivity analysis due to being an outlier on all functional connectivity measures. This resulted in a sample of 17 HCs and 17 SZ patients.

3.2.1 Left inferior frontal gyrus (iFG) functional connectivity

The seed based PLS analysis of functional connectivity with the left iFG ROI identified two significant LVs. The first LV ($p<0.001$) explained 65.1% of the variance, but did not separate the groups or conditions and so was disregarded. The second LV ($p=0.02$) explained 12.9% of the variance and separated mental and physical conditions in the SZ group (see figure 3). The LV identified functional connectivity between the left iFG and the left precuneus, right superior frontal gyrus, right inferior frontal gyrus, right medial frontal gyrus, and the right cingulate gyrus, during mental animations in the SZ cohort. During the physical animations, the left iFG was functionally connected with the right posterior cingulate, left putamen, right culmen, and right superior frontal gyrus (see table 4 and figure 4).

3.2.2 Left caudate functional connectivity

The seed based PLS analysis of functional connectivity with the left caudate ROI identified two significant LVs. The first LV explained 52.0% of the variance ($p<0.001$), but did not separate the groups or conditions and so was disregarded. The second LV ($p=0.01$) explained 17.3% of the variance and separated mental from physical conditions in the SZ group (see figure 5). The LV identified functional connectivity between the left caudate and the right parahippocampal gyrus, right paracentral lobule, and left middle temporal gyrus during mental animations and increased local connectivity in the left caudate during physical animations (see table 4 and figure 6).

Table 4. Regions of functional connectivity with the left inferior frontal gyrus and left caudate nucleus seeds during mental and physical animations

	Peak region	MNI coordinates			voxels	Ratio
		x	y	z		
Left IFG seed						
LV2						
Physical (SZ)	R Posterior cingulate	18	-61	15	623	5.23
	L Putamen	-18	0	-9	42	5.00
	R Culmen	7	-40	-21	47	3.64
	R Sup frontal gyrus	18	11	-9	34	3.62
Mental (SZ)	L Precuneus	-7	-54	57	104	6.76
	R Sup frontal gyrus	11	11	54	869	6.03
	R Inf frontal gyrus	32	14	-21	38	4.67
	R Med frontal gyrus	14	32	39	80	4.35
	R Cingulate gyrus	11	-43	48	35	4.30
Left Caudate Nucleus seed						
LV2						
Physical (SZ)	L Caudate nucleus	-4	11	0	144	20.55
Mental (SZ)	R Parahippocampal gyrus	25	-22	-18	1499	6.63
	R Paracentral lobule	7	-32	51	234	5.45
	L Mid temporal gyrus	-54	-50	-6	49	4.12

Ratio = salience/SE ratio from bootstrap analysis

*** Figures 3-6 approx here ***

3.3 Behavioural PLS results

The behavioural PLS analysis of functional connectivity with the left iFG during mental animations identified one significant LV (p<0.001). The LV explained 70.57% of the variance and identified functional connectivity with the left iFG was associated with greater accuracy for the mental animations (see figure 7). However, this was only significant in the SZ group. The LV identified connectivity between the left iFG and the right iFG and left transverse temporal gyrus (see table 5 and figure 8). All other task-based or seed-based PLS LVs were not significantly associated with accuracy on the mental condition.

Table 5. Regions of functional connectivity with the left inferior frontal gyrus associated with increased performance on the mental condition

	Peak region	MNI coordinates			Voxels	Ratio
		x	y	z		
LV1						
	L Inf frontal gyrus	-40	29	-3	824	-32.10
	R Inf frontal gyrus	47	32	-6	1705	-22.41
	L Transverse temporal gyrus	-50	-18	9	237	-10.11

Ratio = salience/SE ratio from bootstrap analysis

*** Figures 7 and 8 approx here ***

3.4 Association with Full-scale IQ

Although, as expected, HCs scored significantly higher for FSIQ, this was not associated with any of the task-based or functional connectivity LVs within groups or in the combined sample.

4.0 Discussion

In the current study we identified a common network recruited by both healthy controls and patients with schizophrenia that separated the viewing of mental animations from animations involving a physical or random interaction. A seed-based PLS functional connectivity analysis identified different patterns of connectivity with the left iFG and the left caudate nucleus during mental and physical animations in the patients with schizophrenia. The behavioural analysis revealed poorer performance in patients with schizophrenia in identifying the type of interaction, with a specific deficit in the animations involving an interaction that required attributing mental states. Behavioural PLS identified increased functional connectivity between the left and right inferior frontal gyri to be positively associated with accuracy on the mental condition.

The regions involved in the network activated during mental interactions consisted of clusters with peaks in the left and right inferior frontal gyrus, left superior temporal gyrus, right postcentral gyrus, and left caudate nucleus. Regions activated during the physical animations (and random in SZ patients) included the right medial frontal gyrus and the left superior frontal gyrus. The inferior frontal gyri and left superior temporal gyrus involvement supports previous studies employing the Triangles Task (Das, Calhoun, et al., 2012; Das, Lagopoulos, et al., 2012) as well as results from a meta-analysis into similar mentalizing tasks (Schurz, Radua, Aichhorn, Richlan, & Perner, 2014). Additionally, the left iFG is considered a key region of the mirror neuron system with a role in social cognition (Iacoboni, et al., 2005; Uddin, et al., 2007). The increased modulation of activity within the bilateral inferior frontal gyri in patients with schizophrenia supports previous evidence of hyperactivation in frontal regions during social judgments (Mukherjee, et al., 2014). It is interesting to note that we found increased modulation of activation in regions including the left iFG and STG, previously found to be under-activated in schizophrenia using the same task (Das, Lagopoulos, et al., 2012). This is likely due to the explicit responding required in the current study, compared to the implicit nature of the task used previously. Forcing a response may have resulted in greater attention to discerning the animation type, resulting in greater activity in patients due to inefficient neural processing (Potkin, et al., 2009) and again points to differences in implicit and explicit social processing (Frith & Frith, 2006). Another source of difference in the current study also was the inclusion of both males and females, whereas only males were included in the Das et al (2012) study. The association between the physical or goal oriented condition and the activity in the ventral mPFC supports a role for this region in motion complexity and animacy (Kuzmanovic, et al., 2014) and provides evidence for the importance of including this condition into fMRI analyses of the Triangles Task.

Schizophrenia has been described as a disorder of connectivity (Schmitt, Hasan, Gruber, & Falkai, 2011). Therefore, it is not surprising to identify different patterns of functional connectivity in the schizophrenia patients during the Triangles Task. While the connectivity pattern for the healthy controls remained relatively consistent across conditions, patients showed additional connectivity with the left iFG and left caudate nucleus during the physical and mental animations. The increased functional connectivity between the left iFG and other frontal regions during the mental animations in patients with schizophrenia is consistent with previous reports (Das, Calhoun, et al., 2012; Jeong, Wible, Hashimoto, & Kubicki, 2009) and suggests inefficient frontal network segregation may explain difficulties on mental judgment tasks. This is further evidenced by the association between accuracy on the mental animations and functional connectivity primarily between the left and right inferior frontal gyri, but also involving the left temporal lobe. Increased functional connectivity with the caudate nucleus may be a result of antipsychotic medication (Kraguljac, et al., 2016; Sarpal, et al., 2015), especially with the hippocampal region (Kraguljac, et al., 2016), and future studies should explore this association further using social cognitive tasks.

Multivariate approaches similar to the one used in the current study may also prove useful in understanding the onset of psychosis and the links with mentalizing ability. As the Triangles Task is part of the social cognition battery used in the Human Connectome Project (Barch, et al., 2013; Hillebrandt, Friston, & Blakemore, 2014) it is likely to receive considerable attention. Therefore understanding the deficits of clinical groups such as those with schizophrenia and the underlying neurophysiological differences is of paramount importance. The task also has the potential to influence other large collaborative studies, with a potential role in imaging genetics projects due to its ease of use across a broad range of intellectual capabilities and potential as an endophenotype or biomarker (Martin, Robinson, Dzafic, Reutens, & Mowry, 2014).

The current study is limited by its use of a heterogenous sample of chronic, medicated schizophrenia patients. Future studies may wish to look at mentalizing tasks before medication or include medication history as a mediator. The extensive medication history of the current sample made this inappropriate and likely misleading. A larger sample would result in greater power to detect further significant LVs and explain more of the variance in the task, both for task-based and functional connectivity analyses. As functional connectivity is unable to address directionality of effects, studies employing effective connectivity measures, such as dynamic causal modeling, may further our understanding of social cognitive deficits in schizophrenia and the underlying neural differences. However, the current study adds to our understanding and provides valuable advances for such studies to be based.

In sum, the current study suggests that patients with schizophrenia have increased activation in mentalizing regions, including inferior frontal gyri and superior temporal gyri bilaterally, and caudate nucleus during explicit mentalizing judgments. Different functional connectivity patterns were also identified in patients with schizophrenia, with accuracy associated with left iFG connectivity. Overall, schizophrenia is associated with reduced mentalizing ability that is reflected by differences in underlying social brain functioning. This provides further evidence that schizophrenia is a disorder of connectivity, with particular relevance for understanding the social difficulties experienced.

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Declaration of Interest:

The authors report no conflicts of interest. The authors alone are responsible for the content of this manuscript.

References

Adolphs, R. (2009). The social brain: neural basis of social knowledge. Annu Rev Psychol, 60, 693-716.

Adolphs, R. (2010). What does the amygdala contribute to social cognition? Ann N Y Acad Sci, 1191, 42-61.

Barch, D. M., Burgess, G. C., Harms, M. P., Petersen, S. E., Schlaggar, B. L., Corbetta, M., Glasser, M. F., Curtiss, S., Dixit, S., Feldt, C., Nolan, D., Bryant, E., Hartley, T., Footer, O., Bjork, J. M., Poldrack, R., Smith, S., Johansen-Berg, H., Snyder, A. Z., Van Essen, D. C., & Consortium, W. U.-M. H. (2013). Function in the human connectome: task-fMRI and individual differences in behavior. NeuroImage, 80, 169-189.

Bilder, R. M. (2009). The neuropsychology of schizophrenia circa 2009. Neuropsychology Review, 19, 277-279.

Brune, M. (2005). "Theory of mind" in schizophrenia: a review of the literature. Schizophrenia Bulletin, 31, 21-42.

Burianova, H., & Grady, C. L. (2007). Common and unique neural activations in autobiographical, episodic, and semantic retrieval. Journal of Cognitive Neuroscience, 19, 1520-1534.
Carrington, S. J., & Bailey, A. J. (2009). Are there theory of mind regions in the brain? A review of the neuroimaging literature. Human Brain Mapping, 30, 2313-2335.
Castelli, F., Happe, F., Frith, U., & Frith, C. (2000). Movement and mind: a functional imaging study of perception and interpretation of complex intentional movement patterns. NeuroImage, 12, 314-325.
Das, P., Calhoun, V., & Malhi, G. S. (2012). Mentalizing in male schizophrenia patients is compromised by virtue of dysfunctional connectivity between task-positive and task-negative networks. Schizophr Res, 140, 51-58.
Das, P., Lagopoulos, J., Coulston, C. M., Henderson, A. F., & Malhi, G. S. (2012). Mentalizing impairment in schizophrenia: a functional MRI study. Schizophr Res, 134, 158-164.
Fornito, A., Zalesky, A., & Breakspear, M. (2015). The connectomics of brain disorders. Nat Rev Neurosci, 16, 159-172.
Frith, C. D., & Frith, U. (2006). The neural basis of mentalizing. Neuron, 50, 531-534.
Frith, C. D., & Frith, U. (2008). Implicit and explicit processes in social cognition. Neuron, 60, 503-510.
Gershon, E. S., DeLisi, L. E., Hamovit, J., Nurnberger, J. I., Jr., Maxwell, M. E., Schreiber, J., Dauphinais, D., Dingman, C. W., 2nd, & Guroff, J. J. (1988). A controlled family study of chronic psychoses. Schizophrenia and schizoaffective disorder. Archives of general psychiatry, 45, 328-336.
Gur, R. E., Calkins, M. E., Gur, R. C., Horan, W. P., Nuechterlein, K. H., Seidman, L. J., & Stone, W. S. (2007). The Consortium on the Genetics of Schizophrenia: neurocognitive endophenotypes. Schizophrenia bulletin, 33, 49-68.
Harrington, L., Siegert, R. J., & McClure, J. (2005). Theory of mind in schizophrenia: a critical review. Cogn Neuropsychiatry, 10, 249-286.
Hillebrandt, H., Friston, K. J., & Blakemore, S. J. (2014). Effective connectivity during animacy perception--dynamic causal modelling of Human Connectome Project data. Sci Rep, 4, 6240.
Iacoboni, M., Molnar-Szakacs, I., Gallese, V., Buccino, G., Mazziotta, J. C., & Rizzolatti, G. (2005). Grasping the intentions of others with one's own mirror neuron system. PLoS Biol, 3, e79.
Jeong, B., Wible, C. G., Hashimoto, R., & Kubicki, M. (2009). Functional and anatomical connectivity abnormalities in left inferior frontal gyrus in schizophrenia. Hum Brain Mapp, 30, 4138-4151.
Kalkstein, S., Hurford, I., & Gur, R. C. (2010). Neurocognition in schizophrenia. Current topics in behavioral neurosciences, 4, 373-390.
Kraguljac, N. V., White, D. M., Hadley, N., Hadley, J. A., Ver Hoef, L., Davis, E., & Lahti, A. C. (2016). Aberrant Hippocampal Connectivity in Unmedicated Patients With Schizophrenia and Effects of Antipsychotic Medication: A Longitudinal Resting State Functional MRI Study. Schizophrenia bulletin, 42, 1046-1055.
Kuzmanovic, B., Schilbach, L., Georgescu, A. L., Kockler, H., Santos, N. S., Shah, N. J., Bente, G., Fink, G. R., & Vogeley, K. (2014). Dissociating animacy

processing in high-functioning autism: neural correlates of stimulus properties and subjective ratings. Soc Neurosci, 9, 309-325.
Leckman, J. F., Sholomskas, D., Thompson, W. D., Belanger, A., & Weissman, M. M. (1982). Best estimate of lifetime psychiatric diagnosis: a methodological study. Archives of General Psychiatry, 39, 879-883.
Martin, A. K., Robinson, G., Dzafic, I., Reutens, D., & Mowry, B. (2014). Theory of mind and the social brain: implications for understanding the genetic basis of schizophrenia. Genes Brain Behav, 13, 104-117.
Maxwell, M. E. (1992). Family Interview for Genetic Studies (FIGS): a manual for FIGS. Clinical Neurogenetics Branch, Intramural Research Program, NIMH, Bethesda, MD.
McIntosh, A. R., Bookstein, F. L., Haxby, J. V., & Grady, C. L. (1996). Spatial pattern analysis of functional brain images using partial least squares. NeuroImage, 3, 143-157.
McIntosh, A. R., Chau, W. K., & Protzner, A. B. (2004). Spatiotemporal analysis of event-related fMRI data using partial least squares. Neuroimage, 23, 764-775.
Mehta, U. M., Thirthalli, J., Subbakrishna, D. K., Gangadhar, B. N., Eack, S. M., & Keshavan, M. S. (2013). Social and neuro-cognition as distinct cognitive factors in schizophrenia: A systematic review. Schizophrenia Research.
Mohnke, S., Erk, S., Schnell, K., Romanczuk-Seiferth, N., Schmierer, P., Romund, L., Garbusow, M., Wackerhagen, C., Ripke, S., Grimm, O., Haller, L., Witt, S. H., Degenhardt, F., Tost, H., Heinz, A., Meyer-Lindenberg, A., & Walter, H. (2015). Theory of mind network activity is altered in subjects with familial liability for schizophrenia. Soc Cogn Affect Neurosci.
Mukherjee, P., Whalley, H. C., McKirdy, J. W., Sprengelmeyer, R., Young, A. W., McIntosh, A. M., Lawrie, S. M., & Hall, J. (2014). Altered amygdala connectivity within the social brain in schizophrenia. Schizophrenia bulletin, 40, 152-160.
Nuechterlein, K. H., Barch, D. M., Gold, J. M., Goldberg, T. E., Green, M. F., & Heaton, R. K. (2004). Identification of separable cognitive factors in schizophrenia. Schizophrenia Research, 72, 29-39.
Nurnberger, J. I., Jr., Blehar, M. C., Kaufmann, C. A., York-Cooler, C., Simpson, S. G., Harkavy-Friedman, J., Severe, J. B., Malaspina, D., & Reich, T. (1994). Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. Archives of general psychiatry, 51, 849-859; discussion 863-844.
Pedersen, A., Koelkebeck, K., Brandt, M., Wee, M., Kueppers, K. A., Kugel, H., Kohl, W., Bauer, J., & Ohrmann, P. (2012). Theory of mind in patients with schizophrenia: Is mentalizing delayed? Schizophrenia Research.
Pettersson-Yeo, W., Allen, P., Benetti, S., McGuire, P., & Mechelli, A. (2011). Dysconnectivity in schizophrenia: where are we now? Neurosci Biobehav Rev, 35, 1110-1124.
Potkin, S. G., Turner, J. A., Brown, G. G., McCarthy, G., Greve, D. N., Glover, G. H., Manoach, D. S., Belger, A., Diaz, M., Wible, C. G., Ford, J. M., Mathalon, D. H., Gollub, R., Lauriello, J., O'Leary, D., van Erp, T. G., Toga, A. W., Preda, A., Lim, K. O., & Fbirn. (2009). Working memory and DLPFC inefficiency in schizophrenia: the FBIRN study. Schizophrenia bulletin, 35, 19-31.

Russell, T. A., Reynaud, E., Herba, C., Morris, R., & Corcoran, R. (2006). Do you see what I see? Interpretations of intentional movement in schizophrenia. Schizophrenia Research, 81, 101-111.

Sampson, P. D., Streissguth, A. P., Barr, H. M., & Bookstein, F. L. (1989). Neurobehavioral effects of prenatal alcohol: Part II. Partial least squares analysis. Neurotoxicology and Teratology, 11, 477-491.

Sarpal, D. K., Robinson, D. G., Lencz, T., Argyelan, M., Ikuta, T., Karlsgodt, K., Gallego, J. A., Kane, J. M., Szeszko, P. R., & Malhotra, A. K. (2015). Antipsychotic treatment and functional connectivity of the striatum in first-episode schizophrenia. JAMA Psychiatry, 72, 5-13.

Schmitt, A., Hasan, A., Gruber, O., & Falkai, P. (2011). Schizophrenia as a disorder of disconnectivity. Eur Arch Psychiatry Clin Neurosci, 261 Suppl 2, S150-154.

Schurz, M., Radua, J., Aichhorn, M., Richlan, F., & Perner, J. (2014). Fractionating theory of mind: a meta-analysis of functional brain imaging studies. Neurosci Biobehav Rev, 42, 9-34.

Sporns, O., Tononi, G., & Kotter, R. (2005). The human connectome: A structural description of the human brain. Plos Computational Biology, 1, e42.

Suarez, B. K., Duan, J., Sanders, A. R., Hinrichs, A. L., Jin, C. H., Hou, C., Buccola, N. G., Hale, N., Weilbaecher, A. N., Nertney, D. A., Olincy, A., Green, S., Schaffer, A. W., Smith, C. J., Hannah, D. E., Rice, J. P., Cox, N. J., Martinez, M., Mowry, B. J., Amin, F., Silverman, J. M., Black, D. W., Byerley, W. F., Crowe, R. R., Freedman, R., Cloninger, C. R., Levinson, D. F., & Gejman, P. V. (2006). Genomewide linkage scan of 409 European-ancestry and African American families with schizophrenia: suggestive evidence of linkage at 8p23.3-p21.2 and 11p13.1-q14.1 in the combined sample. American Journal of Human Genetics, 78, 315-333.

Sugranyes, G., Kyriakopoulos, M., Corrigall, R., Taylor, E., & Frangou, S. (2011). Autism spectrum disorders and schizophrenia: meta-analysis of the neural correlates of social cognition. PLoS One, 6, e25322.

Uddin, L. Q., Iacoboni, M., Lange, C., & Keenan, J. P. (2007). The self and social cognition: the role of cortical midline structures and mirror neurons. Trends Cogn Sci, 11, 153-157.

Wechsler, D. (1999). Wechsler Abbreviated Scale of Intelligence (WASI). San Antonio, TX: Pearson.

Highlights

- Explicit mentalizing associated with inferior frontal and superior temporal regions
- Patients with schizophrenia revealed to have greater activation in this network
- Connectivity between the inferior frontal gyri associated with greater accuracy

Figure

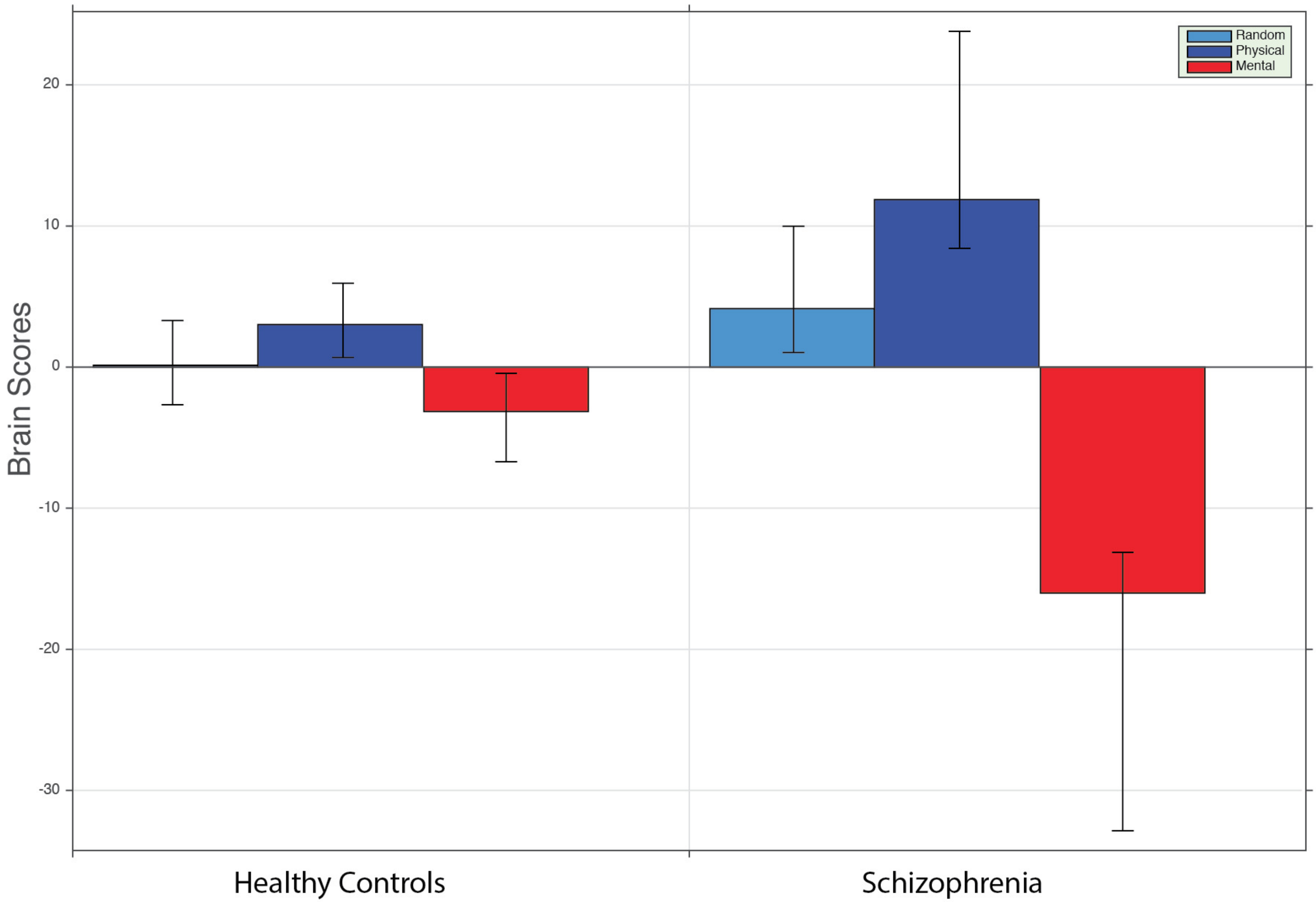

Figure 1. LV1 from the task-based PLS was able to separate mental (red) animations from physical (dark blue) and random (light blue) animations, in patients with schizophrenia (not random for healthy controls).

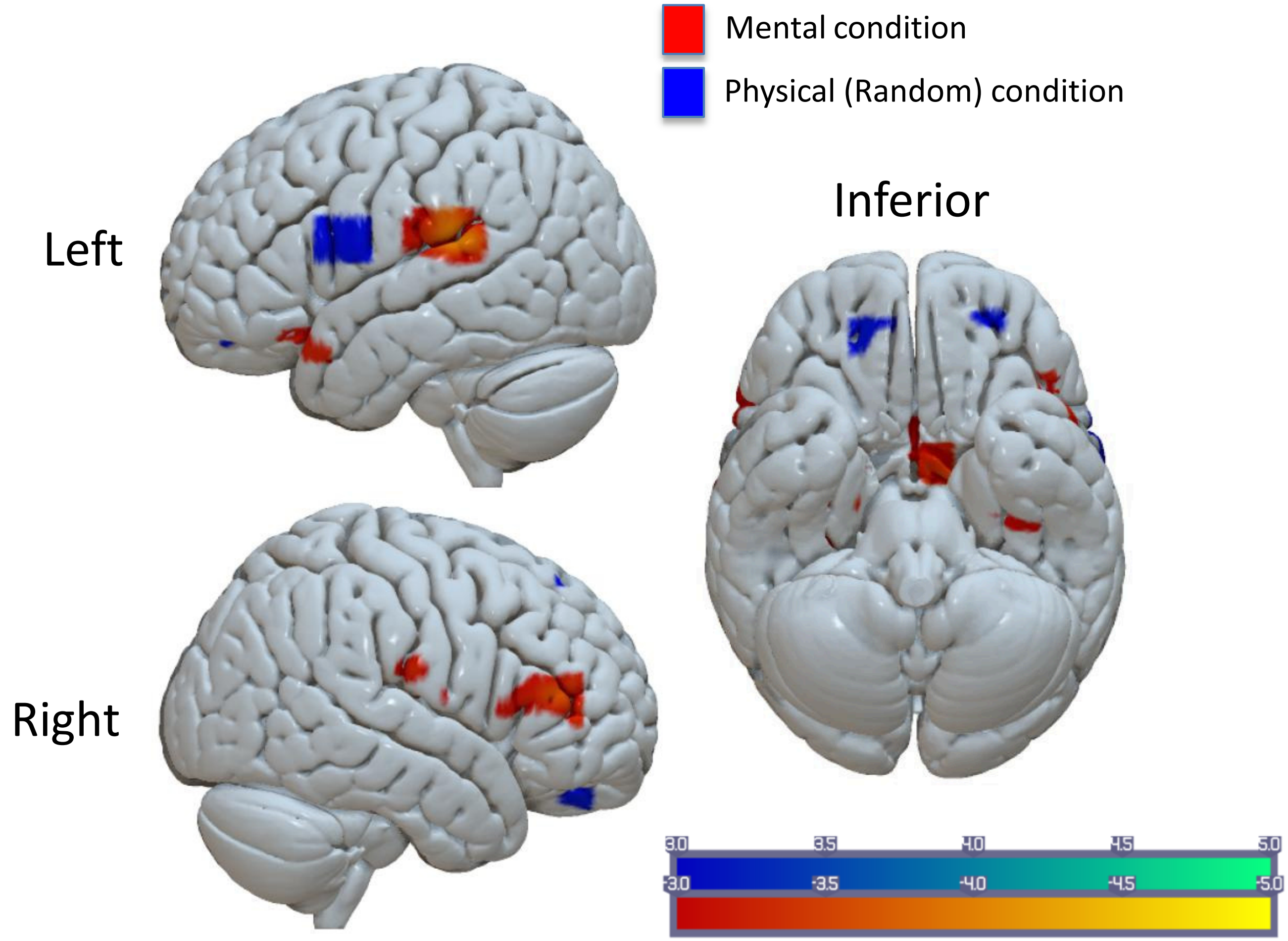

Figure 2. Regions associated with LV1 from the task-based PLS. The random (SZ) and physical (HCs & SZ) animations were associated with activity in the right medial and left superior frontal gyri (blue). Activity in the left and right inferior frontal gyri, left superior temporal gyrus, right postcentral gyrus, and left caudate nucleus was associated with mental animations (HCs & SZ) (red).

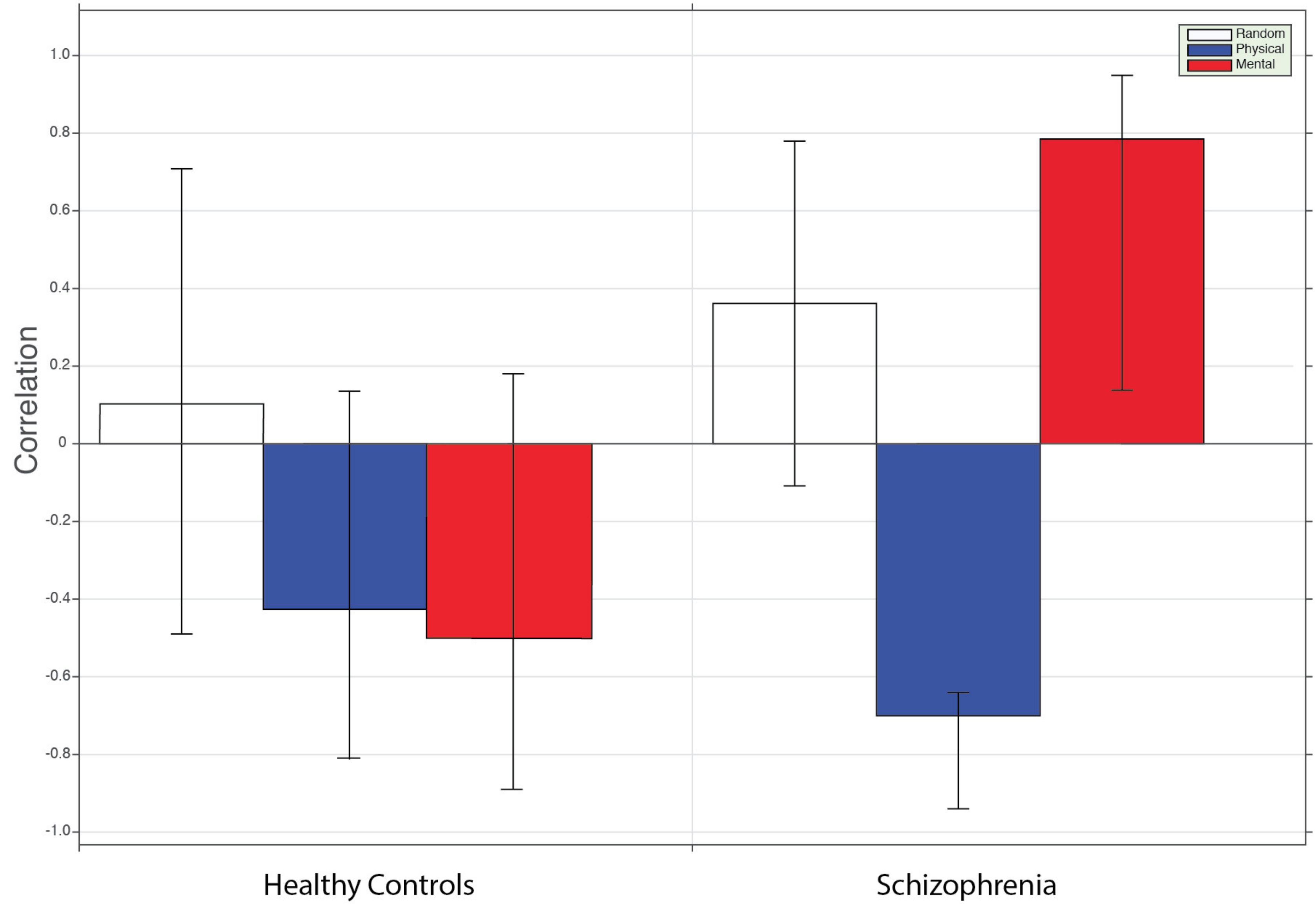

Figure 3. LV2 from the left inferior frontal gyrus seed-based PLS was able to separate mental (red) animations from physical (dark blue) in patients with schizophrenia.

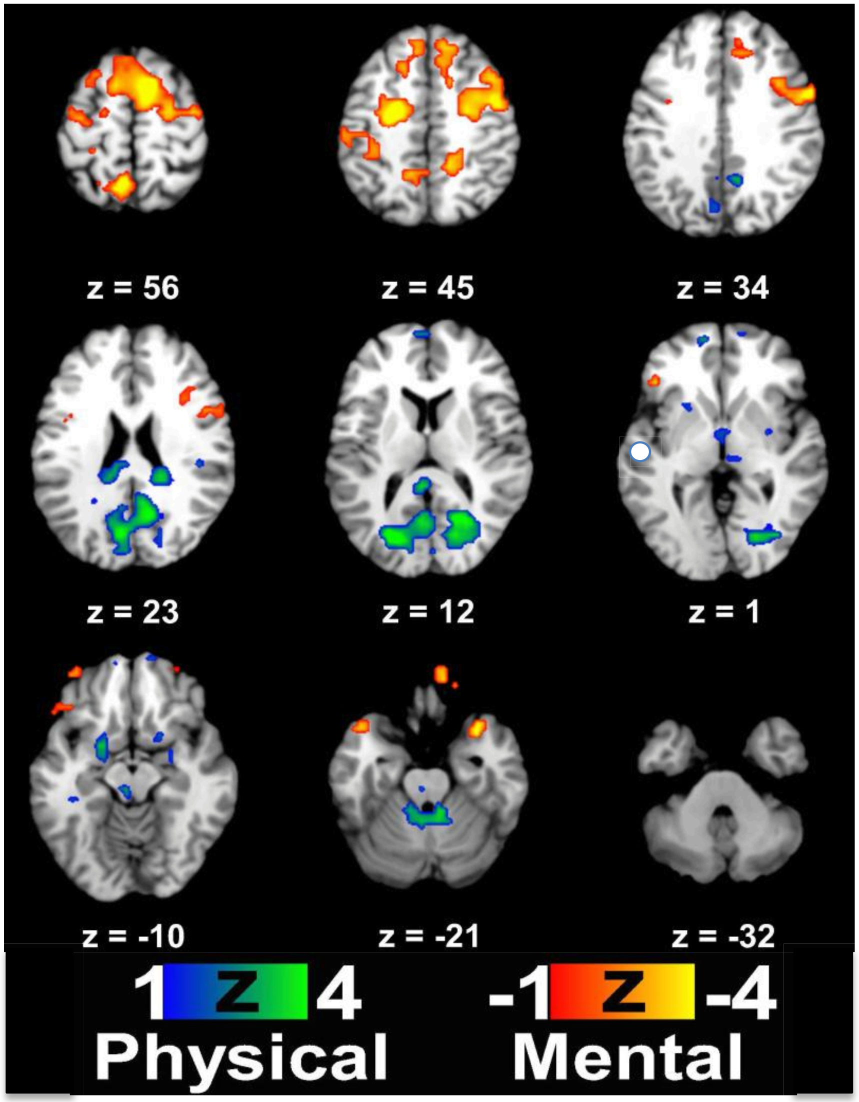

Figure 4. LV2 from the left inferior frontal gyrus seed-based PLS was associated in SZ patients with increased functional connectivity (red) during mental animations with clusters with peaks in the right parahippocampal gyrus, right paracentral lobule, and left middle temporal gyrus. The physical condition was associated with increased local connectivity with the caudate nucleus. The white dot represents the left inferior frontal gyrus seed (approximate).

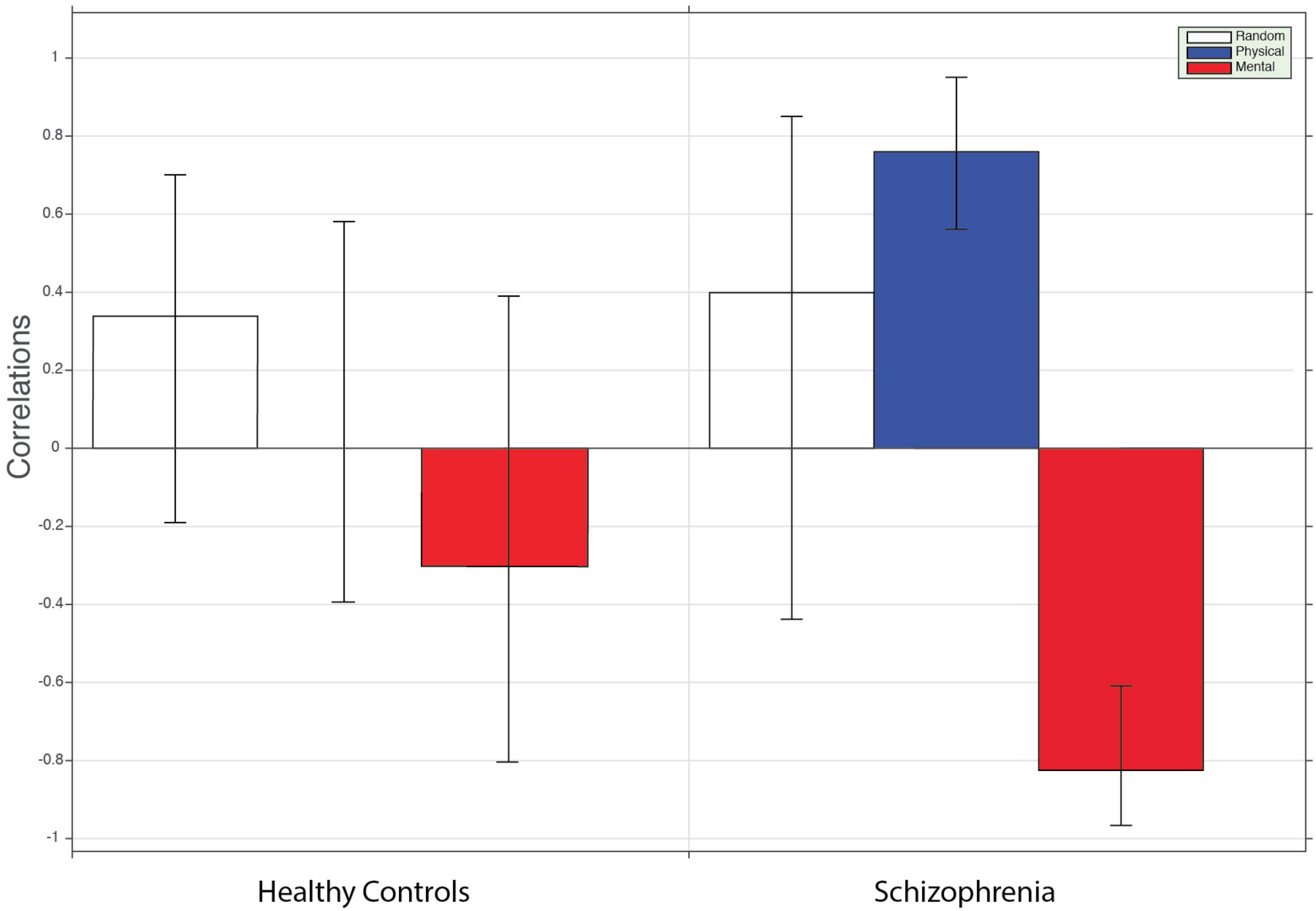

Figure 5. LV2 from the left caudate nucleus seed-based PLS was able to separate mental (red) animations from physical (dark blue) in patients with schizophrenia.

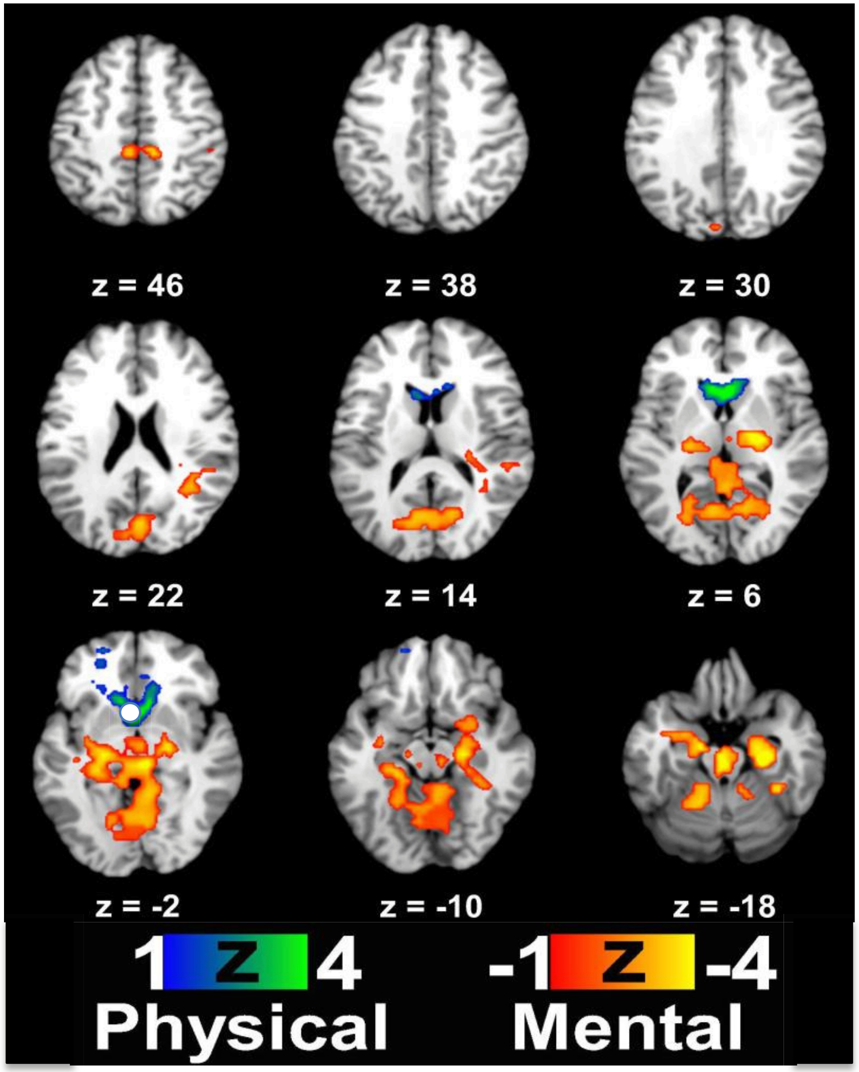

Figure 6. LV2 from the left caudate nucleus seed-based PLS was associated in SZ patients with increased functional connectivity (red) during mental animations with clusters with peaks in the right parahippocampal gyrus, right paracentral lobule, and left middle temporal gyrus. The physical condition was associated with increased local connectivity with the caudate nucleus. The white dot represents the left caudate seed (approximate).

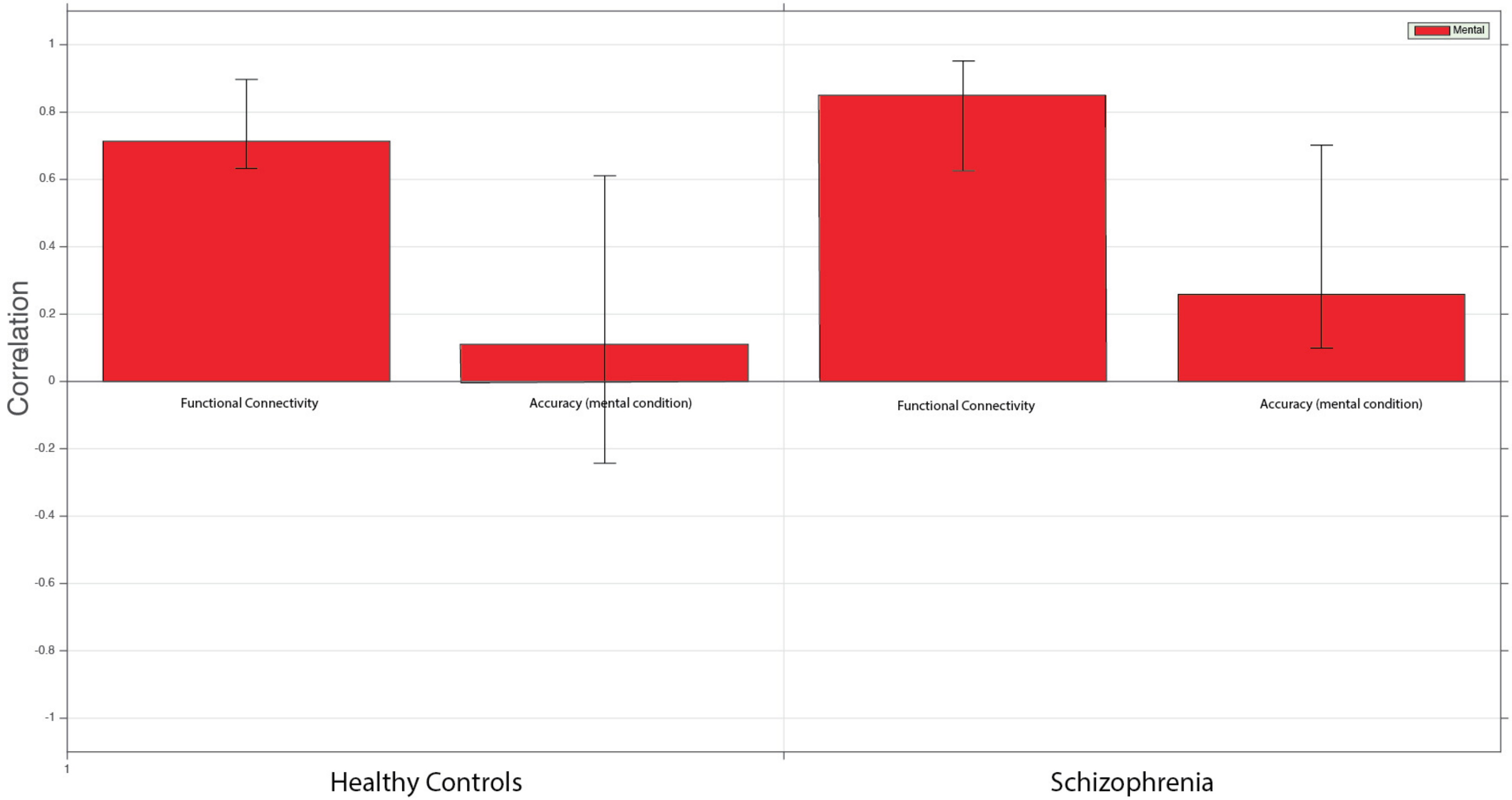

Figure 7. LV1 for the left inferior frontal gyrus functional connectivity from the behavioural PLS with mental accuracy during the mental condition. Accuracy was associated with greater functional connectivity and this was significant in the schizophrenia patients.

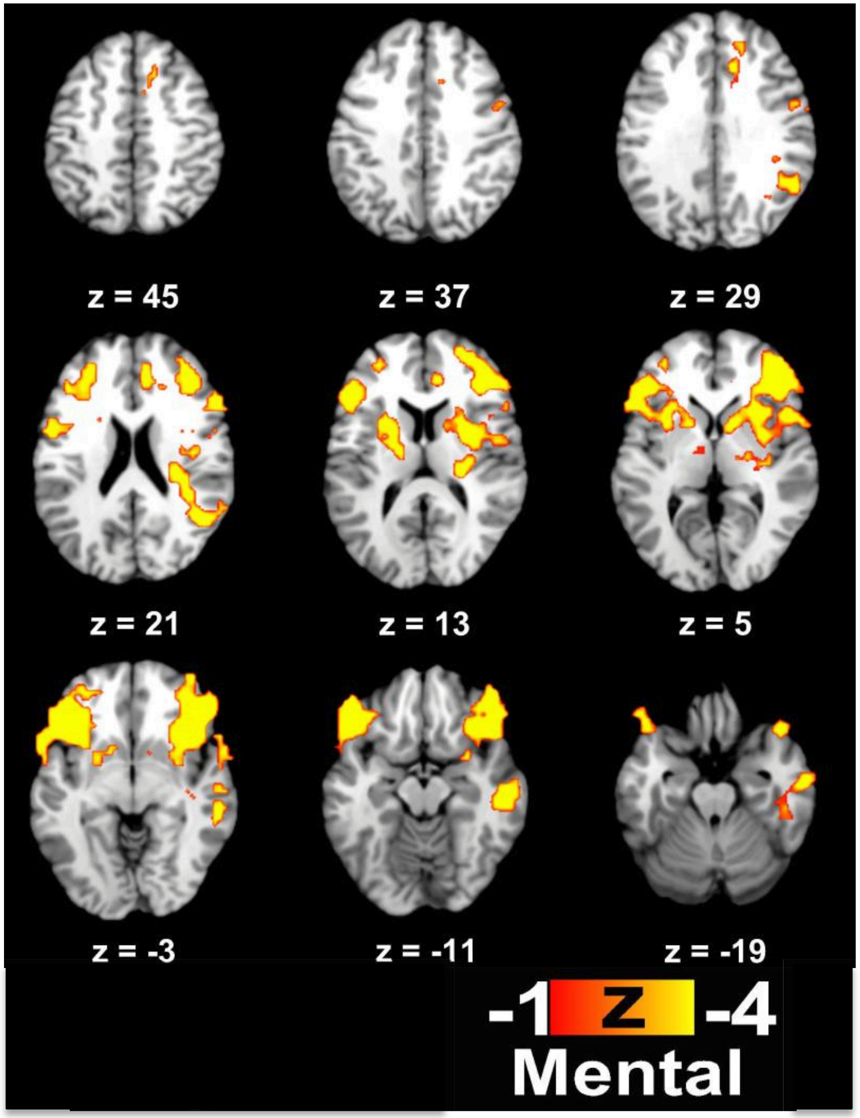

Figure 8. LV1 from the behavioural PLS including the functional connectivity from the left inferior frontal gyrus and including the accuracy for the mental condition. Increased accuracy in patients with schizophrenia was associated with greater functional connectivity between the left and right inferior frontal gyri a cluster with a peak in the left transverse temporal gyrus.