Research Paper

Aberrant network connectivity during error processing in patients with schizophrenia

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Background: Neuroimaging methods have pointed to deficits in the interaction of large-scale brain networks in patients with schizophrenia. Abnormal connectivity of the right anterior insula (AI), a central hub of the salience network, is frequently reported and may underlie patients' deficits in adaptive salience processing and cognitive control. While most previous studies used resting state approaches, we examined right AI interactions in a task-based fMRI study. **Methods:** Patients with schizophrenia and healthy controls performed an adaptive version of the Eriksen Flanker task that was specifically designed to ensure a comparable number of errors between groups. **Results:** We included 27 patients with schizophrenia and 27 healthy controls in our study. The between-groups comparison replicated the classic finding of reduced activation in the midcingulate cortex (MCC) in patients with schizophrenia during the commission of errors while controlling for confounding factors, such as task performance and error frequency, which have been neglected in many previous studies. Subsequent psychophysiological interaction analysis revealed aberrant functional connectivity (FC) between the right AI and regions in the inferior frontal gyrus and temporoparietal junction. Additionally, FC between the MCC and the dorsolateral prefrontal cortex was reduced. **Limitations:** As we examined a sample of medicated patients, effects of antipsychotic medication may have influenced our results. **Conclusion:** Overall, it appears that schizophrenia is associated with impairment of networks associated with detection of errors, refocusing of attention, superordinate guiding of cognitive control and their respective coordination.

Introduction

Schizophrenia is associated with a severe impairment in executive functioning.[1] In particular, patients show deficits in the continuous monitoring of their actions and in the correction of errors.[2] A large body of research has demonstrated these deficits in experimental paradigms, such as the go/no-go task, the Stroop task, or the Eriksen Flanker task.[3,4]

Neuroscientific research has linked these deficits to aberrant functioning of large-scale brain systems.[5] Kopp and Rist[6] found significantly reduced error-related negativity (ERN) in patients with schizophrenia, a finding that later became implied more generally in psychosis.[7,8] Error-related negativity is believed to originate in the midcingulate cortex (MCC),[9] which has been shown to be less active in patients with schizophrenia during conflict, error and novelty processing.[3] More recent studies have emphasized the nosological value of alterations in the concerted activity of large-scale brain networks, such as the salience network ([SN] including the MCC and anterior insula [AI])[10], the central executive network ([CEN] including the dorsolateral prefrontal cortex [DLPFC] and posterior parietal cortex) and the default mode network ([DMN] including the ventromedial prefrontal cortex, posterior cingulate cortex/precuneus and inferior parietal lobule)[11] and the aberrant interaction among these networks.[12]

The AI and MCC have a particularly high risk of being structurally altered in patients with schizophrenia,[13] as grey matter volume in these SN regions is reduced. On the functional level, the SN is conceptualized as crucial for switching between introspection and externally focused attention.[14] This assumption is corroborated by the finding that activity in right AI reliably precedes activation in CEN nodes and deactivation in DMN nodes[14] independent of the experimental paradigm and modality.

Transferring these findings to schizophrenia psychopathology, Palaniyappan and Liddle[15] put special emphasis on the SN's role in updating internal models for context-based action policy selection, initiation and modification. Accordingly,

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activation of the SN is assumed to ensure that the most relevant stimuli receive adequate attention and enables adaptive behaviour by initiating activation of effector regions. Accordingly, its impairment might lead to severe difficulties in allocating attention and adjusting one's behaviour to current allostatic demands.[16] As these are hallmarks of schizophrenia pathophysiology, characterizing SN disruptions may contribute to elucidating various symptoms associated with the disorder. In fact, recent empirical evidence suggests that the biasing of attentional focus via the SN is altered in patients with schizophrenia[17] and may be related to cognitive impairment as well as positive and negative symptoms characteristically associated with schizophrenia.[18–20] A similar difficulty in SN regulation of network activity is also present in high-risk individuals.[21]

Based on resting-state Granger causality analyses, Moran and colleagues[22] report reduced influence of the right AI over activation in the CEN and DMN in patients with schizophrenia and its association with weak cognitive performance. Palaniyappan and colleagues[23] also examined patients with schizophrenia during the resting state and found reduced correlations between activity in insular and dorsolateral prefrontal regions. Based on their results, both studies infer an impaired interaction between the SN and CEN in patients with schizophrenia, namely a weakened influence of the right AI over the CEN and DMN, possibly weakening patients' ability to exert cognitive control in demanding situations. To our knowledge, our study is the first to build on these results and examine SN interactions in a task-based study, as suggested by Moran and colleagues.[22]

Specifically, we used a well-established paradigm of interference control, the Eriksen Flanker task, to assess SN interaction in patients with schizophrenia. As disrupted cingulofrontal interactions in these patients have been implied by several neuroimaging studies,[5] we expected them to show reduced MCC activation in response to errors compared to correct responses. Specifically, we expected this finding even when controlling for the level of cognitive conflict. Crucially, as our design allowed for stratification of within-subjects error rates, our findings cannot easily be explained by differences in motor output or novelty processing. Moreover we assumed that between-groups differences in functional connectivity would emerge for SN seed regions specifically in interaction with error-related activation.

Methods

Participants

We recruited patients with a diagnosis of schizophrenia and healthy controls closely matched for age, sex, education, general intelligence and task performance for participation in our study. The diagnostic status of patients was assessed by 2 experienced psychologists using either the Structured Clinical Interview for DSM-IV (SCID[24]) or the Mini International Neuropsychiatric Inventory (MINI[25]) and was confirmed by a psychiatrist. All included patients satisfied the DSM-IV criteria for schizophrenia, but did not fulfill DSM-IV criteria for an additional axis-I disorder. In particular, there were no signs for any primary mood or anxiety disorders or evidence of schizoaffective disorders. The severity of the patients' symptoms was assessed using the Positive and Negative Syndrome Scale (PANSS).[26] For patients treated with typical or atypical antipsychotics or a combination thereof, we calculated their medication doses in chlorpromazine (CPZ) equivalents based on the method of Gardner and colleagues.[27] Healthy controls were screened for medical, neurologic and psychiatric history. Healthy controls had no history of a DSM-IV psychiatric disorder. Exclusion criteria for all participants were neurologic disorders, in particular a history of seizures or head injury with loss of consciousness, and severe uncontrollable medical conditions that could influence neurocognitive function. All participants gave written informed consent, and the Ethics Committee of the Friedrich-Schiller University approved our study protocol. Patients' ability to give informed consent was independently determined by their primary physicians before recruitment.

Stimuli and task

A modified speeded Flanker task, including an adaptive response deadline as developed by Debener and colleagues,[28] was used to induce a sufficient and comparable number of erroneous responses for each sample. Stimuli were projected onto a screen inside the scanner bore. Following a fixation cross, 5 arrows in horizontal orientation pointing either to the left or to the right were projected onto a mirror attached to the head coil; the arrow in the centre was the target arrow. In 50% of the trials the target arrow pointed in the same direction as the other 4 arrows (compatible condition). In the remaining trials, the target arrow pointed in opposite direction to the distracters (incompatible condition). Each of the 3 runs consisted of 145 trials, with both conditions appearing in pseudorandom order. Stimuli were presented visually with Presentation software version 13.1. Participants were instructed to press a button with their left or right index fingers in accordance with the orientation of the target arrow. It was stressed that response should be issued as quickly and accurately as possible. A performance-adaptive response deadline was implemented to induce sufficient response error rates. It started at 500 ms during training. The deadline was shortened in 10 ms steps down to a minimum of 250 ms if at least 4 of the preceding 6 responses on incompatible trials were correct; it was prolonged in 20 ms steps up to a maximum of 1500 ms if more than 2 of the last 6 responses in the previous array of incompatible or compatible trials were missed. In case of a missed response (i.e., participant provided no response within the time-window), a symbolic feedback was shown instructing the participant to speed up in the next trials. Every participant was given the opportunity to practice the task in an online training run of 15 trials before starting the experiment.

In order to improve estimation of the temporal dynamics of the hemodynamic response function, intertrial intervals were systematically jittered. Specifically, the duration of fixation cross presentation was systematically varied, comprising intervals of 2 pulses in odd-numbered trials and intervals of

3 pulses in even-numbered trials. Additionally, trial onsets were jittered in odd-numbered trials by a value ranging from 0 to repetition time (TR)/2 and in even-numbered trials by a value ranging from TR/2 to TR. Further, we interspersed 11 null event trials during which the fixation cross was shown.

Functional MRI data acquisition, preprocessing and analysis

Functional MRI data were acquired using a 3 T Siemens Magnetom Trio scanner with a standard 12-channel Siemens Head Matrix Coil. Three runs of 373 volumes, each consisting of 35 slices (slice thickness 3 mm, interslice gap 0.50 mm, in-plane resolution 3×3 mm^2) were recorded by means of a T_2*-weighted gradient-echo, echoplanar sequence with a repetition time (TR) of 2300 ms, an echo time (TE) of 30 ms and a flip angle (FA) of 90°, yielding a data matrix of 64×64 voxels within a field of view (FOV) of 192 mm. Acquisition orientation was obliquely tilted approximately 30° relative to the anterior commissure–posterior commissure line.[29] Additionally, a T_1-weighted MPRAGE structural volume in either high (196 slices) or low resolution (96 slices) was recorded for anatomic localization, and a shimming field was applied before functional imaging.

Preprocessing and analysis of the functional data were performed using Brain Voyager QX software (BVQX 1.10 and 2.3, Brain Innovation B. V.). We discarded the first 4 volumes of each run as dummies in order to ensure steady state tissue magnetization. Realignment to the first volume of each run was performed via least squares estimation of 6 rigid body parameters. Further data preprocessing comprised a correction for slice time errors and spatial (8 mm full-width at half-maximum [FWHM] isotropic Gaussian kernel) as well as temporal (high pass filter 8 cycles per run; low pass filter 2.8 s FWHM; linear trend removal) smoothing. Anatomic and functional images were coregistered and normalized to the Talairach space.[30] In addition to controlling for head movements by including them in the general linear model (GLM), we computed summary statistics for the head movement parameters and used them as covariates in an analysis of covariance (ANCOVA). We computed the average root mean squares of motion parameters in every participant (with degrees of rotational parameters converted to millimetres by calculating displacement on the surface of a sphere of 50 mm). We then collapsed the 6 parameters into 1 parameter by calculating their geometric mean. An independent samples t test revealed that there were no significant differences between patients and controls in head motion parameters ($t_{52} = -1.247$; $p = 0.22$).

Extraction of volume of interest (VOI) time courses and convolution with model hemodynamic response functions (HRFs) for psychophysiological interaction (PPI) analyses were conducted using the Neuroelf (www.neuroelf.net) ComputeGLM method. We focused on 3 seed regions tightly linked to schizophrenic pathophysiology by recent reports: the right and left AI and the anterior MCC. These regions were defined a priori based on automated anatomical labelling (AAL) coordinates, as included in the Wake Forest University Pickatlas software,[31,32] and trimmed to their anterior portions in order to better reflect the SN (left and right MCC: $z > 14$; left and right AI: $y < -7$; Fig. 1A). Coordinates comprising these seed regions were transformed to Talairach space using in-house Matlab scripts based on ICBM2Tal. The statistical analysis of fMRI data was based on the GLM with adjustment for autocorrelation following a global autoregressive (AR(1)) model. The stimulation protocols comprised 4 predictors for incompatible and compatible correct and erroneous responses as well as additional predictors of no interest for missed trials, feedback presentation, null events and, in order to account for excess motor activation in schizophrenia, multiple key presses. We derived reference functions based on these protocols. The expected blood oxygen–level dependent (BOLD) signal change for each predictor was modelled by convolving these reference functions with 2-γ HRFs to account for the delayed onset and typical shape of the BOLD signal time course. Using the contrast incompatible error > incompatible correct as a psychological regressor and the respective signal time courses extracted from these 3 seed regions, we calculated 3 PPI-GLMs. Each PPI-GLM therefore contained 2 additional predictors: the signal time course of the VOI and the PPI predictor comprising a convolution of VOI time course and HRFs of the contrast incompatible error > incompatible correct. β-weights for the random-effects group GLM were based on z-standardized time course data and determined by a least squares estimation. We used a cluster-size threshold estimation procedure[33] to correct for multiple comparisons within these search regions. A Monte Carlo simulation based on 1000 iterations determined significant clusters of contiguously activated voxels within these search regions. After setting the voxel-level false-positive rate to $p < 0.005$, uncorrected, and specifying the FWHM of the spatial filter, the simulation resulted in a minimum cluster size (k; range 189–270 mm^3) of contiguously activated voxels corresponding to a false-positive rate of 5%.

Results

Participants

Data were analyzed from 27 patients with a diagnosis of schizophrenia (mean age 36.0 ± 8.7 yr, 8 women) and 27 healthy controls (mean age 33.3 ± 8.2 yr, 9 women) who were closely matched for age, sex, education, general intelligence and task performance. The demographic and clinical characteristics of participants are shown in Table 1. All participants were right-handed. The patients' mean PANSS positive score was 14.7 ± 4.4, and the mean PANSS negative score was 18.4 ± 7.1. Of the 27 patients, 2 were treated with typical antipsychotics, 17 with atypical antipsychotics and 7 with a combination of typical and atypical antipsychotics (mean dose in CPZ equivalents 596.6 ± 330.8 mg/d). One patient was completely unmedicated.

Behavioural results

Participants committed errors in 13.7% of incompatible (schizophrenia 12.5%; controls 14.8%) and 2.0% of compatible trials (schizophrenia 3.2%; controls 0.8%). The adaptive response

deadline algorithm ensured that no significant differences in error frequency emerged between the groups within the incompatible condition: a 2 × 2 ANOVA yielded a nonsignificant group × accuracy interaction ($F_{1,52}$ = 0.004, p = 0.95). Owing to their low number, errors in the compatible condition were excluded from further statistical analyses. Misses occurred in 7.0% of trials (schizophrenia 8.5%; controls 5.5%).

As expected, in the incompatible condition responses on correct trials were slower than responses on error trials, with the schizophrenia group responding slower than controls on both error (360 ms v. 283 ms) and correct trials (440 ms v. 372 ms; Fig. 2A). A 2 × 2 ANOVA of reaction time data revealed significant main effects of group ($F_{1,52}$ = 22.5, p < 0.001) and response condition ($F_{1,52}$ = 428.3, p < 0.001) but no significant

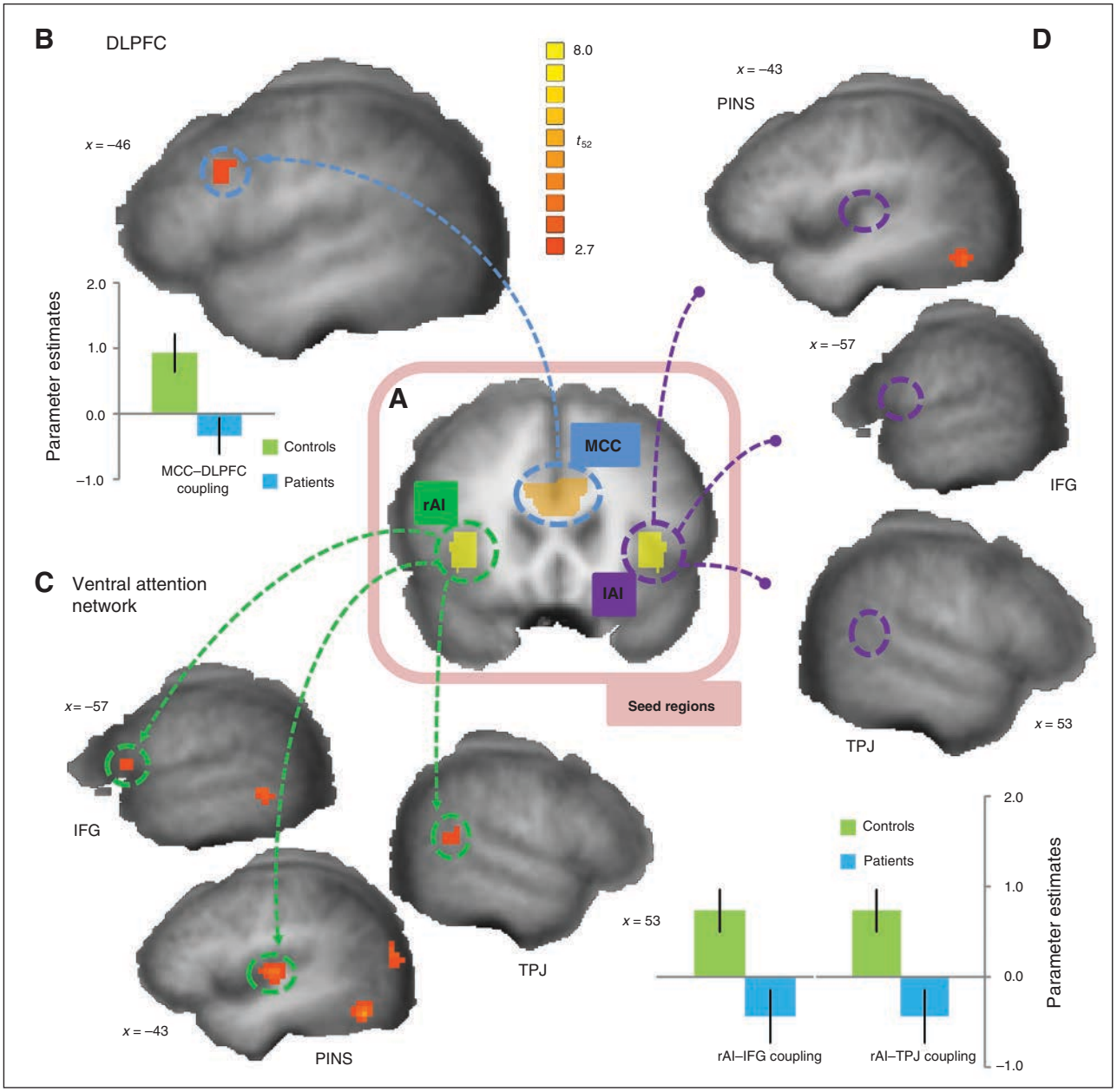

Fig. 1: Group differences in task-based interregional functional connectivity between patients with schizophrenia and healthy controls. Images are in the radiologcial convention. (**A**) Seed regions used in psychophysiological interaction (PPI) analysis: midcingulate cortex (MCC; orange), left anterior insula (lAI; yellow) and right anterior insula (rAI; yellow). (**B**) Top: group differences between patients and controls in functional connectivity of the MCC and dorsolateral prefrontal cortex (DLPFC; blue circles). Bottom: parameter estimates in the DLPFC cluster shown above for PPI seeded from the MCC. (**C**) Left: group differences between patients and controls in functional connectivity of the right AI and the ventral attention network and posterior insula (green circles, clockwise from top: inferior frontal gyrus [IFG], temporoparietal junction [TPJ], posterior insula [PINS]). Right: parameter estimates in the IFG and TPJ clusters shown to the left for PPI seeded from the right AI. (**D**) The same ventral attention regions as shown in **C** do not exhibit significant between-groups differences in functional connectivity when seeded from the left AI.

interaction term ($F_{1,52}$ = 1.3, p = 0.26). The response deadline (averaged across all trials except the first one) differed between patients and controls (491 ± 81.9 ms v. 402 ± 27.4 ms, t_{52} = –5.4, p < 0.001).

Effects of task condition and diagnosis

Across groups, erroneous responses in the incompatible condition were associated with activation in regions of the SN and CEN in comparison to correct responses in the incompatible condition. In these same regions, group comparison revealed significantly (all p < 0.05, corrected) decreased activation in patients with schizophrenia in the MCC (first peak: x, y, z = 6, 23, 31, t_{52} = 5.7; second peak: x, y, z = –6, 20, 34, t_{52} = 5.6), superior and medial frontal gyrus (peak: x, y, z = 15, 8, 64, t_{52} = 5.3), inferior frontal gyrus (IFG; peak: x, y, z = 57, 20, –5, t_{52} = 4.3), precentral gyrus (peak: x, y, z = –39, 8, 1, t_{52} = 5.8) and striatum (peak: x, y, z = 24, 17, 1, t_{52} = 5.1). We found no clusters showing significantly increased activation in patients with schizophrenia (all clusters < 81 mm^3, all t < 2.8, all p > 0.05). We used the BVQX ANCOVA module to test whether group differences in response latency (subject-wise reaction time difference between the incompatible error and incompatible correct conditions) would explain the group differences found in parameter estimates in these same regions (Table 2 and Fig. 2B).

Functional connectivity

Using the contrast incompatible error > incompatible correct as a psychological regressor and signal time courses extracted from the right AI, left AI and anterior MCC, we calculated 3 PPI analyses and tested them for group differences.

Right AI

We found connectivity with the middle temporal gyrus (first peak: x, y, z = –60, –46, –5, t_{52} = 4.4, cluster size 729 mm^3; second peak: x, y, z = –39, –82, 16, t_{52} = 3.6, cluster size 756 mm^3; third peak: x, y, z = 57, –25, –2, t_{52} = 3.4, cluster size 189 mm^3), the temporoparietal junction (TPJ) with a maximum in the superior temporal gyrus (peak: x, y, z = 54, –46, 16, t_{52} = 3.2, cluster size 540 mm^3) and the posterior insula (peak: x, y, z = –42, –13, 7, t_{52} = 4.0, cluster size 1674 mm^3) as well as the inferior frontal gyrus (peak: x, y, z = –51, 17, 13, t_{52} = 3.4, cluster size 324 mm^3) and the adjacent AI (peak: x, y, z = –33, 23, 4, t_{52} = 3.4, cluster size 459 mm^3) to be significantly more pronounced in controls than in patients with schizophrenia (all p < 0.05, corrected). Furthermore, in the parahippocampal gyrus (first peak: x, y, z = –27, –31, –11, t_{52} = 4.2, cluster size 3267 mm^3; second peak: x, y, z = 21, –37, –5, t_{52} = 3.9, cluster size 297 mm^3), the cuneus (peak: x, y, z = –24, –82, 31, t_{52} = 3.3, cluster size 432 mm^3) and bilaterally in several occipital regions within lingual gyrus (first peak: x, y, z = –9, –100, –14, t_{52} = 3.6, cluster size 1674 mm^3; second peak: x, y, z = 15, –94, 23, t_{52} = 3.4, cluster size 297 mm^3) and fusiform gyrus (first peak: x, y, z = –42, –64, –17, t_{52} = 5.5, cluster size 1080 mm^3; second peak: x, y, z = 33, –76, –14, t_{52} = 3.8, cluster size 891 mm^3), FC was also significantly lower in patients with schizophrenia than in controls (all p < 0.05, corrected; Fig. 1C).

Left AI

When seeding PPI-related activation from the AI, we found a region in the posterior thalamus (peak: x, y, z = –15, –31, 4, t_{52} = 3.1, cluster size 513 mm^3) and the left fusiform gyrus (peak: x, y, z = –42, –64, –17, t_{52} = 3.5, cluster size 486 mm^3) to be more strongly associated with the signal time course in the left AI in controls than in patients with schizophrenia (both p < 0.05, corrected). Importantly, however, none of the regions of the ventral attention network functionally coupled to the right AI during error processing was found active in this contrast (all clusters < 27 mm^3, all t < 2.5, all p > 0.05; Fig. 1D).

Anterior MCC

For the MCC seed (Fig. 2B), we found differences in connection strength estimates between groups in the thalamus (peak: x, y, z = –15, –31, 4, t_{52} = 3.43, cluster size 729 mm^3), the cuneus (peak: x, y, z = –3, –79, 34, t_{52} = 3.37, cluster size 270 mm^3) and

Table 1: Demographic and clinical characteristics of patients and controls

	Group; mean ± SD*			
Characteristic	Schizophrenia, n = 27	Controls, n = 27	Statistic	p value
Age, yr	36.0 ± 8.7	33.3 ± 8.2	t_{52} = –1.2	0.25
Sex, male:female	19:8	18:9		
Education level, yr	11.5‡ ± 2.2	11.9‡ ± 1.6	t_{52} = 0.6	0.53
IQ (MWT-B)	112.3§ ± 15.8	114.2 ± 12.5	t_{52} = 0.5	0.63
PANSS Positive	16.5 ± 6.8	—	—	—
PANSS Negative	18.7 ± 6.9	—	—	—
PANSS Psychopathology	37.4 ± 12.0	—	—	—
PANSS Total	72.6 ± 22.6	—	—	—
Chlorpromazine equivalent, mg†	596.6 ± 330.8	—	—	—

MWT-B = multiple-choice vocabulary intelligence test; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation.
*Unless otherwise indicated.
†Calculated based on the method of Gardner and colleagues.[27]
‡Data missing for 1 individual.
§Data missing for 2 individuals.

the left middle frontal gyrus (MFG; peak: $x, y, z = -42, 20, 31$, $t_{52} = 3.41$, cluster size 432 mm^3; all $p < 0.05$, corrected).

A posteriori ANCOVAs

We tested for correlations of brain activation data and CPZ dosage as well as PANSS positive, negative and total scores in the schizophrenia sample to assess if any of these covariates influenced between-groups results. In patients with schizophrenia, connectivity estimates between the right and left insula showed a significant negative association with CPZ dosage ($r_{23} = -0.49$, $p < 0.05$) suggesting that error-related connectivity between the right and left insula is associated with a relative decrease in CPZ dosage. Reported connectivity patterns of the other seed regions — left insula and MCC — showed no significant associations with CPZ (all $p > 0.05$,

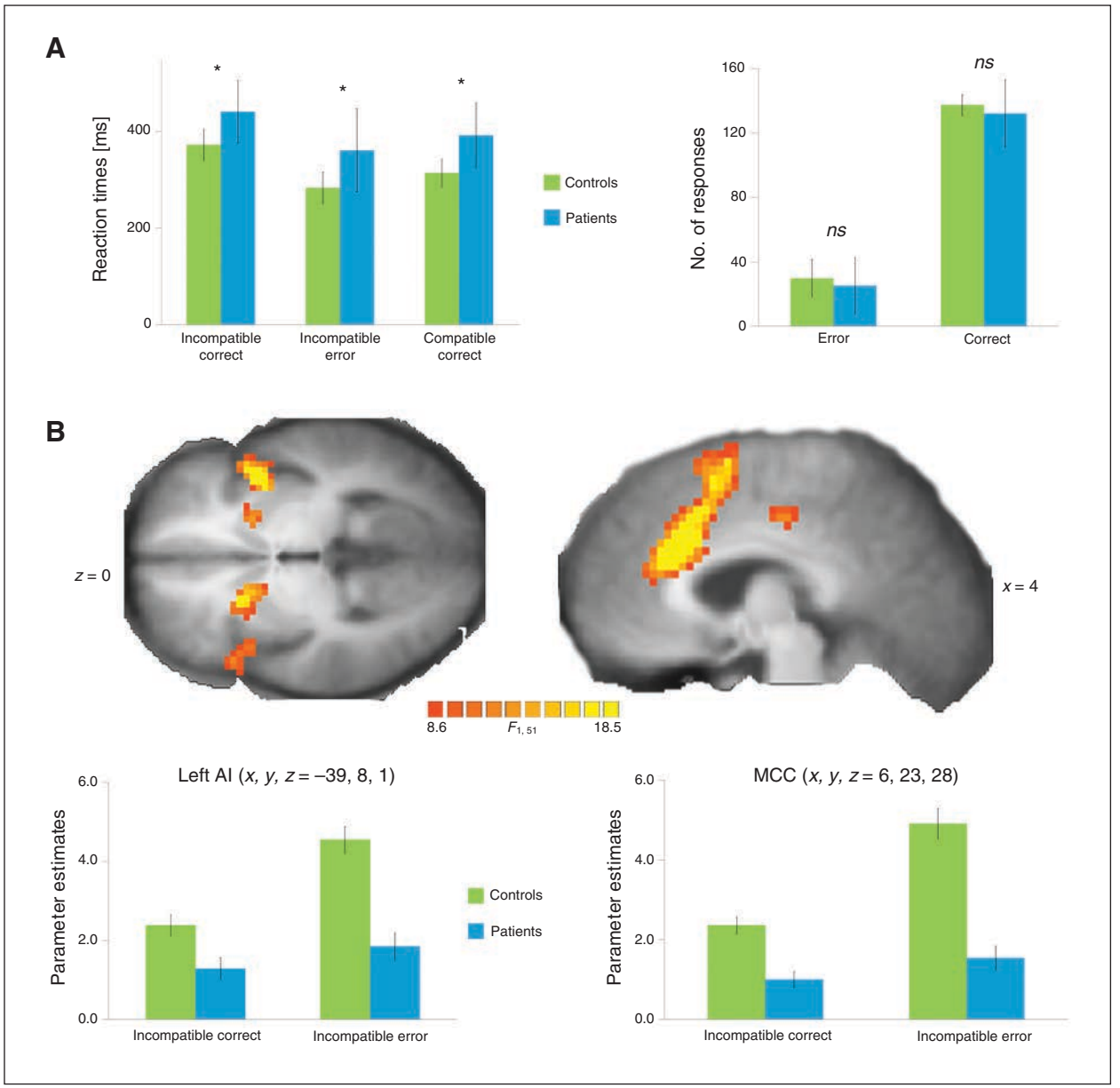

Fig. 2: Flanker effects in behaviour and brain activation of patients with schizophrenia and healthy controls. (**A**) Reaction time data (left) show significant effects of diagnosis and condition on response latency, with patients exhibiting general response slowing. Number of responses (right) indicate that the adaptive response deadline algorithm succeeded in equalizing the number of response error events across groups. (**B**) Between-groups differences in activation to incompatible response errors relative to incompatible correct responses after statistically controlling for individual response time differences (top row). F-maps (top row) show the midcingulate cortex (MCC; right), bilateral insulae and bilateral putamen. Parameter estimate plots (bottom row) are shown for the MCC (right) and left anterior insula (lAI; left). Error bars indicate standard error of the mean. *$p < 0.05$; ns = $p > 0.05$.

corrected). None of the 3 PANSS scores yielded significant associations with brain activation data.

Further, we checked if head motion parameters had an influence on the between-groups results by calculating additional ANCOVAs with these covariates. For every cluster, ANCOVAs with this head motion summary statistic revealed that between-groups results were unaffected by head motion and yielded virtually identical results (all $F > 7.6$, all $p < 0.05$, corrected). For all of these ANCOVAs, we tested for homogeneity of regression slopes across groups and never found this assumption violated (all $F < 2.3$, all $p > 0.10$).

Finally, we tested if group differences in response latency (subject-wise reaction time difference between the incompatible error and incompatible correct conditions) affected PPI results. The ANCOVAs with response latency as a covariate revealed that none of the clusters resulting from PPI modelling were explicable in terms of reaction times (all $F > 8.0$, all $p < 0.05$, corrected). Again, we tested for homogeneity of regression slopes across groups and never found this assumption violated (all $F < 2.0$, all $p > 0.10$).

Discussion

The main goal of our study was to investigate the role of aberrant network functioning, especially of the SN, in patients with schizophrenia while performing a well-established paradigm of interference control, the Eriksen Flanker task. Using event-related fMRI, we replicated the classic finding of reduced MCC activation in patients with schizophrenia during the commission of errors while controlling for confounding factors, such as task performance and error frequency, which have not been explicitly controlled for in most previous studies. Subsequent PPI analysis revealed aberrant task-related connectivity between the nodes of major intrinsic networks, in particular the SN.

On the behavioural level, patients' performance in the Flanker task was comparable to that of healthy controls. Although their responses were slower, the application of an adaptive individual response deadline ensured that patients did not make more errors than controls. This is an important prerequisite for the interpretation of our physiologic data, as group differences in BOLD response cannot unequivocally be attributed to differences on the neural level if (simultaneously) behavioural performance is significantly different between groups.[34,35]

Modelling of error responses under consideration of individual reaction time differences confirmed reduced MCC activity in patients with schizophrenia during error commission. Alterations of MCC response in patients with schizophrenia have been reported previously in a variety of tasks,[5] including Stroop,[3,36] antisaccade,[37] stop- and go/no-go tasks.[38] The most common interpretation of this finding relates to the assumption of deficient performance monitoring processes, in particular regarding detection of error/conflict, in patients with schizophrenia.[3] However, the MCC is known to respond not only to errors or conflict, but also to novel or infrequent events.[39] Though previous studies have tried to statistically control for this finding, many studies that reported reduced MCC activation in patients with schizophrenia could not sufficiently rule out error frequency as a contributing factor to their results.[3,37,40] Sambataro and colleagues[4] addressed this problem by analyzing only correct trials in a modified Flanker paradigm, thereby neglecting erroneous responses completely. Our results complement their findings by showing that patients have reduced BOLD responses in the MCC during error commission even if error rates (and the expectation of errors) are comparable to controls. Thus, our study corroborates the notion of impaired performance monitoring in patients with schizophrenia and extends it by ruling out an uneven distribution of errors as an alternative explanation for impaired MCC activity.

Furthermore, we were able to demonstrate significant alterations in functional connectivity in patients with schizophrenia during error commission. Based on empirical findings suggesting dysfunctional interaction of intrinsic brain networks in patients with schizophrenia, in particular the SN, we conducted PPI analyses with seed regions in the right AI, left AI and MCC.

Table 2: Whole-brain group differences in activation between patients with schizophrenia and controls for the contrast incompatible error > incompatible correct after controlling for between-subjects differences in reaction times*

		Talairach coordinates					
Region	Hemisphere	*x*	*y*	*z*	Brodmann area	Statistic	No. of voxels†
Cingulate gyrus	R	6	23	31	32	$F_{1,51} = 29.2$	417
Cingulate gyrus	L	–6	20	34	32	$F_{1,51} = 28.4$	15 (local max)
Superior frontal gyrus	R	15	8	64	6	$F_{1,51} = 24.3$	158 (local max)
Medial frontal gyrus	L	0	11	49	6	$F_{1,51} = 19.2$	8 (local max)
Medial frontal gyrus	L	–6	5	70	6	$F_{1,51} = 17.2$	14 (local max)
Precentral gyrus	L	–39	8	1	13	$F_{1,51} = 30.7$	37
Lentiform nucleus	R	24	17	1	Putamen	$F_{1,51} = 24.4$	44
Cingulate gyrus	L	–6	–28	40	31	$F_{1,51} = 17.5$	10
Cingulate gyrus	R	3	–16	40	24	$F_{1,51} = 16.9$	33
Inferior frontal gyrus	R	57	20	–5	47	$F_{1,51} = 23.5$	26
Middle frontal gyrus	L	–30	41	25	10	$F_{1,51} = 18.1$	19

L = left; R = right
*ANCOVA results thresholded at $p < 0.001$, and cluster size 10 functional voxels (of $3 \times 3 \times 3$ mm^3).
†One voxel comprises a volume of 27 mm^3.

In patients, we found reduced interactions between the right AI and regions in the IFG as well as temporal lobe areas. Alterations in frontotemporal[41] and frontoparietal connectivity in patients with schizophrenia are well established across a wide variety of tasks and methodological approaches.[42] Our findings relate to regions involved directly in attentional processing: the IFG and TPJ. The IFG is considered a key component for top–down control processes. Lesions in this region lead to impaired performance in tasks of interference control[43] and response inhibition.[44] Moreover, the IFG has been linked to attentional switching or the reallocation of attentional focus.[45,46] Corbetta and colleagues[47] identified the IFG as a major node of the ventral attention system. Acting in concert with the AI and regions in the TPJ, this system takes the role of a "circuit breaker," interrupting ongoing action selection processes in order to gate the processing of behaviourally relevant stimuli in the environment. Weakened connectivity between major nodes of this network (right AI, IFG and TPJ), as observed in our data, may therefore have severe consequences for adaptive refocusing of attentional resources. Specifically, in patients with schizophrenia the right AI appears to be less effective in establishing an orienting response toward errors[48] that would allow for an adjustment of strategies according to current demands. Thus, errors may be a less salient and less informative event for patients, impairing their ability to monitor and adjust their behaviour accordingly. These results support previous findings of impaired SN function [22,23] and show that weakened influence of the right AI in patients with schizophrenia is not restricted to the resting state, but is also present in the online processing of cognitive tasks.

The MCC seed region in patients has decreased connectivity with the left DLPFC (Brodmann area [BA] 9) and left thalamus (pulvinar) during error commission. The DLPFC is a key structure for many top–down control processes, biasing information processing according to contextual information, current goals and plans.[49,50] Interactions between the MCC and DLPFC are believed to be of crucial importance for the implementation of cognitive control. Some authors[51] have hypothesized that the MCC detects conflict (errors being a special case of conflict), triggering the upregulation of top–down control exerted in the DLPFC. Although activations of both the MCC and DLPFC are frequently reported in interference control paradigms,[52] direct evidence for such causal interaction remains sparse.[40,53,54]

In patients with schizophrenia, reduced activity of both the DLPFC and MCC has been observed on a regular basis.[5] Increased interactions between the 2 sites in patients with schizophrenia were reported by Sambataro and colleagues.[4] Our results, however, show decreased interaction, which may be due to fundamental differences between the contrasts entered into the analysis, age-related or medication-related effects.[42] However, both studies point to an underlying deficit in MCC–DLPFC circuitry, which may have important consequences for the processing of errors. Assuming that the MCC has a key role in the neural circuitry involved in the detection of errors, whereas the DLPFC is more involved in subsequent adjustment of control processes, the deficient coupling between the 2 sites suggests a severe impairment in the adaptation of neurocognitive processing strategies to changing demands.

This deficit adds to the aforementioned abnormalities in right AI coupling. Taken together, it appears that schizophrenia is associated with impairment of the systems devoted to the detection of errors (MCC), the refocusing of attention (IFG, TPJ), the superordinate guiding of cognitive control (DLPFC) and their respective coordination. Importantly, the differences in BOLD response reported here cannot easily be accounted for by between-group differences in error frequency or novelty processing, as we stratified error rates between groups.

Limitations

Our study is constrained by several factors that have important implications for the interpretation of our data. First, we examined a sample of medicated patients who were on a stable dose of antipsychotics. While the effect of antipsychotics on BOLD response may vary depending on various factors, such as D2 binding affinities,[55] there is some evidence that antipsychotic medication affects neurophysiologic correlates of performance monitoring. In particular, there is evidence that ERN (and thus probably activity in the anterior MCC) can be reduced under antipsychotic medication.[56–58] As the majority of our clinical sample was treated with antipsychotic medication we cannot rule out that some of the results obtained in our study may have been influenced by effects of medication. Second, owing to the relative infrequency of errors in the compatible condition (i.e., low conflict trials) in patients with schizophrenia, only errors in the incompatible condition (i.e., high conflict trials) entered the analysis. Even though our design controlled for the potentially confounding effect of the level of response conflict, a closer investigation of different error types would elucidate the specificity of the observed reduced connectivity to errors.

Conclusion

We have presented findings that support the assumption of aberrant functioning of the right AI in patients with schizophrenia. Our own approach differs from that of former studies by using BOLD responses acquired during a speeded response task and not during extended resting periods adapting seed-based analyses to an event-based protocol. Further, we have shown that abnormal response of the MCC to errors in patients with schizophrenia is not due to group differences in task performance, but remains significant even after controlling for error rates and individual reaction times.

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