

Teasing Apart the Impact of Illness and IQ on Functional Neuroimaging Findings in Schizophrenia

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Abstract

Schizophrenia is a major psychiatric disorder associated with cognitive impairment. Functional brain imaging (fMRI) studies of schizophrenia patients reveal a complex pattern of brain differences in the prefrontal cortex. Both decreased (hypofrontality) and increased (hyperfrontality) activity have been reported in patients – inconsistencies that this paper argues could be explained by differences in IQ between patients and healthy controls. This study demonstrates a novel method to tease apart IQ and schizophrenia effects on brain activity. Twelve schizophrenia patients were matched to twelve healthy controls matched to patients' estimated (premorbid) IQ *before* their illness, and twelve healthy controls matched to patients' measured *current* IQ. All participants performed an executive function event-related fMRI task. Schizophrenia patients' mean behavioral scores fell numerically between those of both control groups, and did not differ significantly from either group. Two distinct patterns of brain activity were found that were consistent with an

effect due to either IQ impairment or schizophrenia diagnosis. Schizophrenia patients' relatively *reduced* activity in middle/superior frontal (BA6/BA8) regions was related to their schizophrenia diagnosis, whereas their relatively *increased* activity in inferior frontal (BA44/45) and left middle frontal (BA8/9) regions related instead to their current IQ impairment. These findings indicate that some fMRI differences reported in schizophrenia patients are artefacts of IQ matching. After removing the IQ confounds, schizophrenia was associated with lateral frontal hypoactivations and medial frontal failure of de-activation. This paper proposes a method to address IQ matching-related issues when studying populations where their illness involves cognitive deterioration.

Keywords: FMRI, Schizophrenia, IQ, Executive function, Default mode network

Introduction

Schizophrenia is a major psychiatric disorder associated with varying degrees of generalized cognitive impairment, including lower IQ relative to healthy controls (Palmer, Dawes, & Heaton, 2009; Vöhringer et al., 2013). Functional brain imaging (fMRI) shows schizophrenia is also associated with a complex pattern of abnormal brain activity in the prefrontal cortex when patients perform certain attention-demanding cognitive tasks. The classical functional imaging finding in schizophrenia is 'hypofrontality'; for example one meta-analysis shows that there is reduced resting or task-related activity in the prefrontal cortex, particularly in the dorsolateral prefrontal cortex (Hill et al., 2004). However, over the last decade it has become increasingly evident that the pattern of frontal activation abnormality in schizophrenia is more complicated than this. In particular, studies have also reported regions of relative hyperactivity, in the ventrolateral and medial regions of prefrontal cortex during cognitive task performance (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009; Tan, Callicott, & Weinberger, 2007).

The frontal lobes carry out so-called executive functions, a range of higher order cognitive abilities that enable individuals to strategically plan and execute goal-directed behaviors, and evaluate whether or not goals are being attained (Baddeley, 1986; Norman & Shallice, 1986). Many patients with schizophrenia show a deficit in executive function. However this deficit is part – albeit a prominent part – of a pattern of generalized intellectual impairment that varies in severity from patient to patient, but which is on average similar to the levels seen in patients with neurological disorders affecting brain function (Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005; Heinrichs & Zakzanis, 1998). This generalized deficit typically shows itself in a reduction

of around 15 points between estimated premorbid IQ and current IQ (Reichenberg, 2010; Seidman, Buka, Goldstein, & Tsuang, 2006).

For this reason, and since performance on cognitive tasks is correlated with IQ (Mackintosh, 2001), it is important to make sure that IQ is similar in patient and healthy control groups to avoid differences on functional imaging that simply reflect patients' general tendency to intellectual impairment. In schizophrenia studies, patients and healthy controls are typically matched on premorbid IQ. That is, patients' estimated level of intellectual function *before* they became ill (their premorbid IQ) is matched with the *current* IQ of the healthy controls. This estimation of patients' premorbid IQ (and healthy controls' IQ) is usually arrived at via a proxy measure such as years of education, or more accurately by means of standardized tests of vocabulary or the ability to pronounce irregular words (both of which have been found empirically to be relatively resistant to intellectual decline, e.g. Schoenberg et al. (2017)). This form of IQ matching however, will inevitably overestimate patients' *current* cognitive abilities, because the patients' current IQ will be lower than their premorbid IQ (Leeson et al., 2011). More importantly, these current IQ differences (between the patients and healthy controls) could lead to spurious brain imaging differences. In fact, studies have reported brain activations correlated with IQ scores in healthy controls in the prefrontal cortex (Duncan, Burgess, & Emslie, 1995; Gray, Chabris, & Braver, 2003). The authors on this paper have previously demonstrated IQ-related fMRI differences during executive functioning in several prefrontal (and other) brain regions (between groups of healthy individuals who significantly differed in IQ points but were matched in terms of their age and education level) (Graham et al., 2010). Notably these IQ-related brain regions shared several overlaps with those where differences have been reported between schizophrenia patients and healthy controls in several previous neuroimaging studies comparing schizophrenia patients and healthy controls.

The alternative strategy would be to match patients and controls on current IQ. This is considered hazardous in neuropsychology however, because it assumes that the current IQ of a patient whose cognitive ability has declined from a higher level can be equated with the IQ of a healthy subject who always had this level of IQ - something that is clearly not the case (Lezak, Howieson, Bigler, & Tranel, 2012). Either way, the fact that there are IQ differences between schizophrenia patients and controls, and that IQ has functional imaging correlates, means that some or possibly even all of the previously reported fMRI differences between patients and healthy controls could actually be due to IQ differences rather than presence of schizophrenia.

To investigate this possibility, the current study examined patients with the disorder and two groups of healthy controls: one control group matched to the patients' pre-morbid IQ and the other control group matched to the

patients' current IQ. Logically, using this method makes it possible to determine whether any brain region that shows a difference between patients and healthy controls is related to IQ differences or instead to the diagnosis of schizophrenia per se. For example, if a brain region were affected by IQ then the imaging values for the schizophrenia patients in this brain region would be expected to fall within the imaging values of the premorbid IQ matched healthy controls (who represent the estimated upper bound of the patients' IQ) and the imaging values of the current IQ matched healthy controls (who represent the estimated lower bound of the patients' IQ). That is, the imaging values for the patient group should fall in between or close to either of the control groups. The imaging values of the two control groups in this brain region would also be expected to differ because of the IQ difference between the two control groups. Conversely, if a brain region were affected by schizophrenia, the pattern of imaging values should be such that both groups of healthy controls are similar to each other (reflecting a region unaffected by IQ differences), and also different from the patients.

Methods

Participants

Twelve patients (6 males) with schizophrenia (tested within 5 years of presentation; mean current IQ estimated via Wechsler Abbreviated Scale of Intelligence score = 98 ± 12 standard deviation; mean premorbid IQ estimated via Wechsler Test of Adult Reading = 118 ± 8 ; PANSS (Positive = 16 ± 5 , Negative = 16 ± 5 , General = 30 ± 8) were compared with 12 (6 males) premorbid IQ-matched healthy controls (mean IQ = 122 ± 9) and 12 (5 males) current IQ-matched healthy controls (mean IQ = 98 ± 5). All participants were right-handed and matched for age and years of education. All patients were medicated (eight with Risperidone, three with Olanzapine, one with Chlorpromazine). Control participants did not have a first-degree relative with schizophrenia. No participants had current IQ below 85 or recent drug/alcohol abuse or neurological disorders. The study protocol was approved by the local institutional ethics committee (Domain Specific Review Board, National Healthcare Group, Singapore) and written informed consent was obtained prior to participation. In the case of the patients, the ability to give informed consent was assessed by the referring psychiatrist.

Imaging Task

All participants performed an event-related set shifting executive function fMRI task adapted from the Wisconsin Card Sort Test (WCST) during functional blipped gradient echoplanar imaging on a Siemens (Erlangen, Germany) 1.5T Symphony MRI scanner (TR=3000 ms; flip angle = 90° ; 64x64 pixel matrix; FOV=192x192 mm). Each run consisted of 156

whole brain acquisitions (32 axial descending interleaved 3 mm slices, 0.3 mm gap) acquired parallel to the line between the anterior and posterior commissures.

Participants were given a brief exposure to the task before entering the scanner to ensure that performance differences were not attributable to misunderstandings about sorting criteria or the concept of sorting itself (Stuss et al., 1983). During response selection, five cards appeared on a blue screen. Four equally spaced reference cards appeared along the top of the screen and remained unchanged throughout the experiment (Graham, 1999). A target card appeared centrally and was to be matched with one of four reference cards, according to a randomly selected rule (color, shape, or number). The target card was never identical to a reference card, but shared the same color, shape or number of composite items. The participant was allowed 4s in which to respond, otherwise the words “too late” would appear and the trial would terminate. Following the participant’s response, a bar appeared under the chosen reference card. At the end of the 4s period, the stimuli disappeared and were replaced by fixation (a white cross centred on a blue background). After a further 5s (9s since the start of the trial), the feedback stimulus appeared in white letters centred on the blue background: “Right” or “Wrong” for correct or incorrect responses, respectively. The feedback stimulus appeared for 500ms, the display then changed to fixation until the onset of the next trial. Variable periods of fixation (3s, 6s or 9s) were inserted between trials to allow sufficient separation and jittering of trials to facilitate deconvolution. The average trial onset asynchrony was 14s. The first presentation of positive feedback (“1stPF”) was a cue to update the cognitive set with the newly discovered rule. After a random number of between two and four further successive correct feedback (“2+PF”) events during which the participant maintained the known rule, another rule was randomly selected by the computer (at this stage unknown to the participant). The participant’s next response (based on the previous rule) would result in negative feedback – the first negative feedback (“1stNF”) with the new rule which gave the participant the opportunity to realize that the rule had changed and to take appropriate action. All other trials on which negative feedback was presented were considered to be subsequent negative feedback (“2+NF”) events. The number of maintenance (2+PF) trials was intentionally lowered from ten to between four and six (randomly determined to make the shift trial unpredictable) in order to mitigate their over-representation in the general linear modelling of the imaging data (GLM), and to allow more events of other types to contribute to the average of their respective regressors; previous work by the authors has shown elsewhere that this methodology is effective and valid (Graham, 1999; Graham et al., 2010). Thus a “set loss” was defined as an error after three

successive correct trials in the absence of a dimension change. Each scanning session consisted of five runs, each lasting eight minutes.

Image data analysis

The functional images were processed (slice scan time and motion correction, 8mm FWHM spatial smoothing, linear trend removal), registered to the T1-weighted anatomical reference (MPRAGE; 240 slices, 1 mm isovoxel) and transformed into Talairach space prior to computation of a hierarchical random effects general linear model with separate regressors (corrected for serial correlation) for each condition relative to a fixation baseline using Brain Voyager QX (Version 2.3, Brain Innovation, Maastricht, Holland). Each regressor was convolved with a canonical haemodynamic response function (HRF) peaking 6 s after presentation onset of the card stimuli or feedback respectively. Jittering the fixation interval between feedback evaluation and the ensuing response selection aided in the deconvolution of events. Furthermore, the variable nature of the feedback (sometimes positive, other times negative) and the separation of first and subsequent instances of each event type, ensured that the specific type of response selection and feedback evaluation were not correlated in time. The hierarchical GLM analysis entailed a first level analysis in which all experimental conditions for each subject were modelled as separate regressors. The resulting GLM thus contained eight regressors per subject: 1stNF, RS1stNF, 2+PF, RS2+PF, 1stPF, RS1stPF, 2+PF, and RS2+PF. Each regressor was then analyzed at the second-level using separate group-level random-effects t-tests: patients versus premorbid-IQ matched controls; patients versus current-IQ matched controls, and premorbid-IQ versus current-IQ matched controls. The resultant group-level statistical parametric t-maps were corrected for multiple comparisons using cluster-size thresholding (Forman et al., 1995; Goebel, Esposito, & Formisano, 2006). Briefly, each map was initially thresholded at a voxel-wise p-value ($p < 0.03$ uncorrected) that yielded distinct segregated regions of interest (ROIs) and then subjected to a whole-brain (no mask) correction criterion based on the estimate of the map's spatial smoothness (the FWHM was estimated by BVQX to be 1.417 in native voxel resolution) using 1,000 iterations of Monte Carlo simulation to determine the minimum cluster size threshold (ranging from 473 mm³ to 1197 mm³). These cluster-size thresholds were then applied to the group-level statistical t-maps to yield a corrected 5% false positive rate. Voxels activated above the indicated threshold ($p < 0.05$ corrected) were selected and the peak of activation for each ROI was reported. The inclusion of a fixation baseline also allowed the estimation of HRF predictors for each of these conditions of interest for each group of participants. Thus, whenever significant differences were detected between any two groups in the statistical t-maps, the z-

normalized regressor values (averaged across all voxels in the ROI) for each condition for each group were then extracted from each ROI and plotted relative to the fixation baseline for added information (see Figure 1).

Results

Schizophrenia patients' mean behavioral performance (\pm standard deviation) did not differ significantly from that of Premorbid-IQ or Current-IQ matched controls on total number of rules identified (20.0 ± 3.7 , 21.5 ± 2.1 , 18.5 ± 3.0 respectively), errors per shift (2.4 ± 0.7 , 2.1 ± 0.3 , 2.8 ± 0.9 respectively), set losses (2.2 ± 2.1 , 1.3 ± 1.5 , 3.5 ± 2.5 respectively) or reaction times (1770 ± 394 ms, 1515 ± 248 ms; 1884 ± 220 ms respectively).

Group fMRI differences at each of the four feedback and four response selection conditions (see Table 1) revealed regions-of-interest (ROIs) from which the imaging regressors for each condition were extracted. In the interest of focusing on the implications of the methodological concept being advanced here and not introducing unnecessary complexity, the discussion here is

limited to imaging differences observed in the frontal lobes. Significant between-group imaging differences for each of the eight imaging regressors are listed in Table 1 (Feedback conditions) and Table 2 (Response Selection conditions).

Table 1

Feedback Conditions	Patients vs. Prem-IQ				Patients vs. Curr-IQ				Prem-IQ vs. Curr-IQ			
	x	y	z	mm ³	x	y	z	mm ³	x	y	z	mm ³
1stNF Controls > Patients												
Left Middle Frontal Gyrus (BA 11)	-30	49	-13	2178	-	-	-	-	-30	47	-14	1873
Right Middle Frontal Gyrus (BA 11)	35	49	-14	2065	-	-	-	-	-	-	-	-
Medial Frontal Gyrus (BA 9)	-	-	-	-	±3	44	27	721	-	-	-	-
Cingulate Gyrus (BA 24/32)	-7	30	24	3250	-	-	-	-	-	-	-	-
Medial Frontal/Subcallosal Gyrus (BA 11/25)	7	25	-13	3638	5	22	-12	994	-	-	-	-
Right Insula/Inferior Frontal Gyrus (BA 13/47)	32	21	-4	1286	-	-	-	-	-	-	-	-
Right Superior Frontal Gyrus (BA 8)	13	21	48	4760	-	-	-	-	-	-	-	-
Left Middle Frontal Gyrus (BA 8/9)	-46	19	33	1402	-	-	-	-	-	-	-	-
Right Middle Frontal Gyrus (BA 6)	32	10	35	1110	-	-	-	-	-	-	-	-
1stNF Patients > Controls												
Cingulate/Medial Frontal Gyrus (BA 10/32)	-	-	-	-	9	48	-5	1935	±10	47	-5	4801
2+NF Controls > Patients												
Medial Frontal Gyrus (BA 9)	±4	48	30	1817	±3	49	27	588	-	-	-	-
Cingulate Gyrus (BA 24/32)	-3	30	26	2387	-3	32	26	568	-	-	-	-
Left Superior Frontal Gyrus (BA 8)	-18	24	42	2102	-17	24	41	760	-	-	-	-
Right Superior Frontal Gyrus (BA 8)	13	22	47	2775	17	24	50	501	-	-	-	-
Left Middle Frontal Gyrus (BA 8/9)	-46	16	37	3797	-	-	-	-	-46	18	34	1378
Right Middle Frontal Gyrus (BA 6)	32	6	40	1269	-	-	-	-	-	-	-	-
1stPF Controls > Patients												
Left Middle Frontal Gyrus (BA 11)	-33	47	-14	1458	-	-	-	-	-34	46	-14	2768
Right Middle Frontal Gyrus (BA 11)	21	39	-18	738	-	-	-	-	20	44	-18	2436
Medial Frontal/Subcallosal Gyrus (BA 11/25)	±3	30	-19	1922	3	30	-11	1135	-	-	-	-
Cingulate Gyrus (BA 24/32)	±2	31	27	712	±3	32	30	2400	-	-	-	-
1stPF Patients > Controls												
Right Medial Frontal Gyrus (BA 10)	16	61	-5	1089	11	62	4	1868	-	-	-	-
Left Inferior Frontal Gyrus (BA 44/45)	-42	20	8	1151	-	-	-	-	-	-	-	-
2+PF Controls > Patients												
Medial Frontal Gyrus (BA 9)	5	46	27	1197	±4	48	27	1438	-	-	-	-
Right Middle Frontal Gyrus (BA 11)	17	43	-18	3613	-	-	-	-	-	-	-	-
Left Middle Frontal Gyrus (BA 11)	-32	46	-16	2480	-	-	-	-	-	-	-	-
Medial Frontal/Subcallosal Gyrus (BA 11/25)	5	25	-11	1876	±5	29	-13	2152	-	-	-	-
Left Middle Frontal Gyrus (BA 6)	-43	5	37	3114	-	-	-	-	-	-	-	-
Right Middle Frontal Gyrus (BA 6)	34	10	31	5831	-	-	-	-	-	-	-	-

Table 1 fMRI imaging group contrasts for each of the four feedback conditions. Note. “Patients” denotes patients with schizophrenia; “Prem-IQ” denotes premorbid-IQ matched healthy controls; “Curr-IQ” denotes current-IQ matched healthy controls; 1stNF = first negative feedback; 2+NF = subsequent negative feedback; 1stPF = first positive feedback; 2+PF = subsequent positive feedback; BA = Brodmann Area; x y z = Talairach coordinates (x, y, z); mm³ = cluster size in mm³

Table 2

Response Selection Conditions	Patients vs. Prem-IQ				Patients vs. Curr-IQ				Prem-IQ vs. Curr-IQ			
	x	y	z	mm ³	x	y	z	mm ³	x	y	z	mm ³
RS1stNF Controls > Patients												
Right Insula/Inferior Frontal Gyrus (BA 13/47)	42	32	-3	849	38	28	-5	1505	-	-	-	-
Cingulate Gyrus (BA 24/32)	±4	33	17	1442	±5	33	17	3799	6	33	16	1227
Cingulate Sulcus (BA 24/32)	-	-	-	-	-13	14	33	2802	-13	13	34	628
Left Middle Frontal Gyrus (BA 8/9)	-46	15	40	1524	-	-	-	-	-46	25	36	750
Left Superior Frontal Gyrus (BA 8)	-19	22	42	1306	-20	24	42	2834	-	-	-	-
Right Superior Frontal Gyrus (BA 8)	-	-	-	-	11	24	47	573	-	-	-	-
Left Middle Frontal Gyrus (BA 6)	-36	2	36	606	-37	5	36	1764	-	-	-	-
Right Middle Frontal Gyrus (BA 6)	35	8	36	1009	36	5	36	906	-	-	-	-
RS1stNF Patients > Controls												
Right Inferior Frontal Gyrus (BA 44)	49	8	21	772	-	-	-	-	48	9	25	4494
Left Inferior Frontal Gyrus (BA 44/45)	-42	22	11	1068	-	-	-	-	-	-	-	-
Right Precentral Gyrus (BA 4)	37	-22	61	4754	-	-	-	-	-	-	-	-
RS2+NF Patients > Controls												
Right Inferior Frontal Gyrus (BA 44)	44	7	27	1939	-	-	-	-	45	6	28	1300
Left Inferior Frontal Gyrus (BA 44)	-48	6	22	2294	-	-	-	-	-	-	-	-
Right Precentral Gyrus (BA 4)	37	-22	62	5142	35	-15	57	2452	-	-	-	-
RS1stPF Controls > Patients												
Left Middle Frontal Gyrus (BA 6)	-	-	-	-	-38	12	34	1818	-	-	-	-
Right Insula/Inferior Frontal Gyrus (BA 13/47)	38	18	-1	2013	38	23	2	1387	-	-	-	-
Left Medial Frontal Gyrus (BA 6)	-4	-4	63	1747	-	-	-	-	-3	-4	63	534
RS1stPF Patients > Controls												
Right Precentral Gyrus (BA 4)	39	-22	61	2477	-	-	-	-	-	-	-	-
RS2+PF Controls > Patients												
Cingulate Gyrus (BA 24/32)	-	-	-	-	±5	36	21	3815	-	-	-	-
Right Insula/Inferior Frontal Gyrus (BA 13/47)	37	20	0	3588	38	26	-3	2192	-	-	-	-
Left Superior Frontal Gyrus (BA 8)	-18	20	43	1716	-18	19	45	1407	-	-	-	-
Right Superior Frontal Gyrus (BA 8)	13	20	47	1386	-	-	-	-	-	-	-	-
Right Middle Frontal Gyrus (BA 6)	36	8	36	2245	30	16	44	2774	-	-	-	-
Medial Frontal Gyrus (BA 6)	-5	-2	66	4049	-	-	-	-	-3	-2	65	1011
Left Middle Frontal Gyrus (BA 8/9)	-46	20	38	2213	-	-	-	-	-	-	-	-
Left Middle Frontal Gyrus (BA 6)	-	-	-	-	-35	5	40	2425	-	-	-	-
RS2+PF Patients > Controls												
Right Precentral Gyrus (BA 4)	36	-22	64	5009	30	-22	65	752	-	-	-	-

Table 2 fMRI imaging group contrasts for each of the four response selection conditions. Note. “Patients” denotes patients with schizophrenia; “Prem-IQ” denotes premorbid-IQ matched healthy controls; “Curr-IQ” denotes current-IQ matched healthy controls; RS1stNF = response selection after the first negative feedback; RS2+NF = response selection after subsequent negative feedback; RS1stPF = response selection after the first positive feedback; RS2+PF = response selection after subsequent positive feedback; BA = Brodmann Area; x y z = Talairach coordinates (x, y, z); mm³ = cluster size in mm³

These imaging regressors are also shown (see Figure 1) for selected regions plotted across the eight time-points of the set shifting time course (starting from the first negative feedback (1stNF) through rule identification to rule maintenance (RS2+PF) – orange arrows indicate significant group differences). Two distinct patterns of imaging regressors in these ROIs emerged (see Figure 1). In the first, there were significant differences between the current-IQ matched and the premorbid-IQ matched healthy controls; with patients’ imaging regressors falling in between or close to one of the control groups. This first pattern indicated that imaging differences were related to IQ

(rather than to the diagnosis of schizophrenia). These ROIs were located in left middle frontal (BA8/9; -45, 25, 38), bilateral inferior frontal (BA44/45; $\pm 49, 7, 27$), bilateral middle frontal (BA11; $\pm 30, 45, -15$) and medial frontal (BA6; -4, -1, 63) gyri.

The second set of ROIs were characterized by a pattern of imaging regressors that were similar for both groups of healthy controls and distinct for those of the patients. This second pattern indicated that imaging differences were related to the diagnosis of schizophrenia (rather than IQ impairment). These latter set of ROIs could be further sub-divided into two kinds: (i) those in which patients showed hypoactivation relative to both groups of healthy controls, which was observed in the bilateral middle frontal (BA6; $\pm 35, 10, 36$), the bilateral superior frontal (BA8; $\pm 20, 22, 48$), the medial frontal cortex (BA9; $\pm 4, 48, 27$ - a region that extended ventrally and caudally into the callosomarginal sulcus BA24/32; $\pm 3, 30, 17$), and the right insula/inferior frontal cortex (BA13/47; $39, 21, -3$); (ii) those in which the patients showed hyperactivation relative to controls, as observed in the right medial frontal (BA10/32; $11, 62, 4$) and right precentral (BA4; $37, -22, 61$) cortex

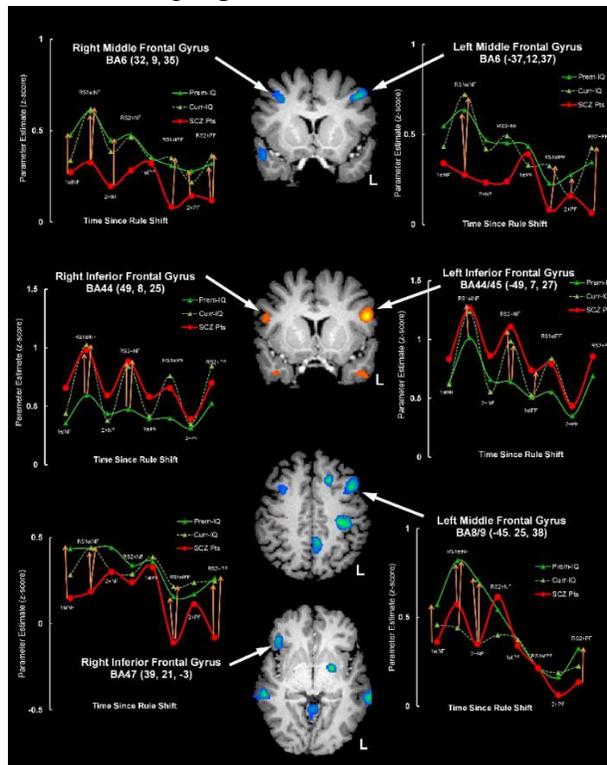


Figure 1 .*Note. “SCZ Pts” denotes patients with schizophrenia; “Prem-IQ” denotes premod-IQ matched healthy controls; “Curr-IQ” denotes current-IQ matched healthy controls; 1stNF = first negative feedback; 2+NF = subsequent negative feedback; 1stPF = first positive feedback; 2+PF = subsequent positive feedback; BA = Brodmann Area; x y z = Talairach coordinates (x, y, z); mm3 = cluster size in mm3*

Discussion

The brain regions where differences were found between schizophrenia patients and controls are consistent with those identified in previous fMRI studies and meta-analyses (see e.g. Minzenberg et al., 2009). The novel use in this study of two control groups matched on estimated premorbid IQ or current IQ enabled prefrontal activation changes due to schizophrenia to be disambiguated from those due to IQ confounds. Using this methodology, prefrontal functional imaging differences specifically related to schizophrenia were characterized by a pattern of hypoactivation in the lateral aspects of the prefrontal cortex (although not, as we find, particularly centred on the dorsolateral prefrontal cortex), as well as hyperactivation in the right ventromedial prefrontal cortex. It is interesting to note that this latter region (BA 10/32) forms part of the default mode network, a group of brain regions which normally de-activate during performance of attention-demanding tasks, and so the findings here probably reflect abnormal de-activation rather than true hyperactivation (the subtractive methodology employed in fMRI studies means that both failure of de-activation and hyperactivation will give the same appearance (Raichle et al., 2001)). This is consistent with converging evidence documenting failure of de-activation of the medial frontal cortex in schizophrenia (Dreher et al., 2012; Pomarol-Clotet, Oh, Laws, & McKenna, 2008; Schneider et al., 2011). Weinberger and co-workers have previously reported task-related hyperactivations in the lateral prefrontal cortex (Callicott et al., 2000; Callicott et al., 2003; Tan et al., 2006). However the present findings suggest that what remains instead when IQ is controlled for in the way we have shown are lateral frontal hypoactivations and medial frontal failure of de-activation.

It can be seen from Figure 1 that the degree of current IQ matching achieved between schizophrenia patients and their healthy controls will also influence the reliability of finding activity differences in the prefrontal cortex. For example, considering the left middle frontal gyri, the hypofrontality in BA6 (-37, 12, 37) is robust to issues in IQ matching, whereas finding hypofrontality in BA8/9 (-45, 25, 38) appears to rely on the presence of a current IQ impairment in the patients relative to their healthy controls. This pattern of findings was evident in other regions (see e.g., Figure 1) and issues in matching IQ between patients and their healthy controls are therefore likely to explain some inconsistencies in previous fMRI studies.

It is interesting to note that the likelihood of finding hypo- or hyperfrontality in patients (relative to healthy controls), also depends on the nature of fMRI task employed, as well as the precise location within the prefrontal cortex. The experimental events which are designed by the experimenter to be the events of imaging interest can influence whether fMRI differences are found between patients and controls. For example, in the

bilateral inferior frontal gyri, patients showed hyperfrontality in the BA44/45 region for response selection events that followed negative feedback (see Figure 1). Both RS1stNF and RS2+NF would involve selecting a response based on a new rule and inhibiting pre-potent but inappropriate response tendencies built up during recent performance with the previous rule. Thus a more difficult fMRI task that emphasized response selection under situations of greater choice uncertainty and increased need for response inhibition would be expected to show hyperfrontality in this region of the ventrolateral prefrontal cortex. Conversely, in the right inferior frontal gyrus (BA47) region of the ventrolateral prefrontal cortex, schizophrenia patients showed hypofrontality for response selection events that followed positive feedback. RS1stPF was the first response after the identity of the new rule was confirmed, and RS2+PF were the responses associated with maintaining the known rule (i.e., responses when choice certainty was higher). Thus an easier task with simple responses would be expected to yield hypofrontality in this region of ventrolateral prefrontal cortex (see Figure 1).

Conclusion

This study's findings indicate that some of the functional imaging changes reported in schizophrenia are artefacts of IQ matching. However, the authors recognize that while the task used in this study attempts to cover a broad spectrum of executive function components, the task was not able to include all the components that IQ conceivably involves. This is one possible limitation that should be taken into account when interpreting our findings.

This limitation notwithstanding, these findings underline the need to take IQ matching in functional imaging studies of schizophrenia more seriously than in studies to date. Specifically, the use of two different control groups – premorbid IQ-matched and current IQ-matched – advanced in this paper provides a practical method to achieve this.

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