**Further evidence of alerted default network connectivity and association with theory of mind ability in schizophrenia**

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**Abstract**

Background: Resting-state functional magnetic resonance imaging (rs-fMRI) has repeatedly shown evidence of altered functional connectivity of large-scale networks in schizophrenia. The relationship between these connectivity changes and behaviour (e.g. symptoms, neuropsychological performance) remains unclear.

Methods: Functional connectivity in 27 patients with schizophrenia or schizoaffective disorder, and 25 age and gender matched healthy controls was examined using rs-fMRI. Based on seed regions from previous studies, we examined functional connectivity of the default, cognitive control, affective and attention networks. Effects of symptom severity and theory of mind performance on functional connectivity were also examined.

Results: Patients showed increased connectivity between key nodes of the default network including the precuneus and medial prefrontal cortex compared to controls (p<0.01, FWE-corrected). Increasing positive symptoms and increasing theory of mind performance were both associated with altered connectivity of default regions within the patient group (p<0.01, FWE-corrected).

Discussion: This study confirms previous findings of default hyper-connectivity in schizophrenia spectrum patients and reveals an association between altered default connectivity and positive symptom severity. As a novel find, this study also shows that default connectivity is correlated to and predictive of theory of mind performance. Extending these findings by examining the effects of emerging social cognition treatments on both default connectivity and theory of mind performance is now an important goal for research.

Keywords: schizophrenia, social cognition, fMRI, default network

Word count: 2,997

**1. Introduction**

Schizophrenia is characterised by deficits in cognitive processes such as working memory and attention (Nuechterlein et al., 2004). These deficits are among the strongest predictors of functional outcome, making better understanding of cognitive deficits an important priority (McGurk et al., 2007; Lewandowski et al., 2011). Theory of mind (TOM) is the ability to attribute thoughts, beliefs and intentions to other people (Van Overwalle, 2009). Schizophrenia patients also show large deficits in TOM (Bora et al., 2009), which predicts 15-50% of variation in social functioning (Roncone et al., 2002; Brüne et al., 2007), suggesting TOM is a particularly important target for new treatments in order to improve social function and rehabilitation.

To examine cognitive deficits at the level of the brain, functional magnetic resonance imaging (fMRI) has been used to identify differences in brain activity in schizophrenia patients compared to healthy controls during performance of cognitive tests (Glahn et al., 2005). Interest in using fMRI data acquired during rest has also grown, in part because data can be obtained in as little as five minutes and does not carry any behavioural demands, which can be stressful for some patients (Whitfield-Gabrieli and Nieto-Castanon, 2012). Neural networks show low-frequency synchronous fluctuations of the blood oxygen-level dependent (BOLD) signal during rest, allowing researchers to examine functional connectivity between different areas of the brain (Whitfield-Gabrieli and Nieto-Castanon, 2012). Several resting-state networks have now been identified, including networks that play an important role in TOM, working memory and attention (Foxet al., 2006; Sheline et al., 2010).

Altered functional connectivity has been consistently observed in schizophrenia patients suggesting it may be a primary factor contributing to illness (Stephanet al., 2009). Functional connectivity has also been shown to explain more variance in behaviour than either brain activity or brain structure, suggesting that connectivity changes may have a particularly strong impact upon behavioural outcomes (Pezawaset al., 2005; Meyer-Lindenberg, 2009). Patients with schizophrenia show altered functional connectivity across several resting-state networks with increased connectivity and spatial extent of the default network the most consistent finding (Whitfield-Gabrieli et al., 2009; Garrity et al., 2007; Zhou et al., 2007).

In order to better understand resting-state connectivity changes in schizophrenia and the relation of these changes to clinical measures of symptom severity, the present study examined each of five networks involved in cognitive functions disrupted in schizophrenia in a sample of 27 patients and 25 healthy controls and effects of positive and negative symptoms, following resting-state fMRI (rs-fMRI) methods previously employed in our group (McCarthy et al., 2013) (see **table 1**). To investigate the relationship between connectivity changes and cognitive function, we also performed a post-hoc analysis examining effects of TOM test scores on connectivity of all networks showing initial differences between patients and controls.

>> Table 1 <<

**2. Materials and methods**

**2.1 Participants**

28 patients with a DSM-IV diagnosis of schizophrenia/schizoaffective disorder were recruited for this study. Participants were right-handed, aged 18-65, had no history of substance abuse in the preceding six months, no previous head injury associated with a loss of consciousness of more than a few minutes and provided written consent in accordance with local ethics committee guidelines. One patient was excluded from the study due to excess movement in the MRI scanner (**section 2.3**), leaving a total of 27 patients. 25 healthy participants that matched the patient group in age and gender were selected from a larger sample of healthy volunteers that were recruited as part of an imaging and cognitive genetics study on psychosis (Mothersill et al., 2014a; Mothersill et al., 2014b).

**2.2 Instruments**

Positive and negative symptoms were measured using the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984) and Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983), where separate symptoms are rated between 0 (absent) and 5 (severe) based on interview with patients. We used SAPS/SANS as they are among the most common symptom rating scales used and have been used in previous rs-fMRI studies on schizophrenia (Whitfield-Gabrieli et al., 2009).

Patients and controls showed significant differences in connectivity between brain regions that play an important role in TOM (**section 3.2**). In a post-hoc analysis, we therefore examined the relationship between TOM and functional connectivity of these regions to better understand effects of these connectivity changes on TOM. To do this, we examined effects of Reading the Mind in the Eyes test score (Baron‐Cohen et al., 2001) on connectivity of all seed regions showing patient-control differences. Participants had to verbally identify the correct mental state of individuals from four possible answers from visual inspection of 36 black and white photographs of the eye region of the face. We used the Eyes test because it is a sensitive measure of TOM, schizophrenia patients consistently show large deficits in Eyes performance (Bora et al., 2009) and it has previously been associated with increased precuneus and TPJ activity under fMRI (Baron-Cohen et al., 1999; Schurz et al., 2014).

For this analysis we focussed on patients, given that we were primarily interested in examining effects of dysconnectivity on behavioural performance in schizophrenia. In addition, only a small number of healthy controls had data available for this test (N = 11 / 25) compared to the patient group (N = 20 / 25).

**2.3 Procedures**

First, SAPS and SANS were administered to patients as part of our larger study on psychosis prior to recruitment for MRI scanning and were assessed by clinical researchers. A printed version of the Eyes test was also administered to patients by a member of the research team separately to the MRI scan. Finally, the MRI scans were performed as part of a longer MRI assessment in the Trinity College Institute of Neuroscience for our larger study on psychosis.

**2.4 MRI acquisition parameters**

Participants were scanned using a Philips Intera Achieva 3-T MRI scanner with a SENSE 8-channel head coil. We acquired whole-brain BOLD EPI with 35 3.5 mm slices, TR = 2000 ms, TE = 30 ms, field of view = 224 x 224 mm, flip angle = 90°. Before functional MRI scanning, participants were asked to close their eyes and relax for approximately six minutes.

Structural images consisted of a T1-weighted image (180 slices; duration: 6 minutes) acquired using a TFE gradient echo pulse sequence, with slice thickness of 0.9 mm, a 230 × 230 mm field of view and a spatial resolution of 0.9 × 0.9 × 0.9 mm3.

**2.5 MRI data pre-processing**

Spatial pre-processing of the fMRI data was carried out using Statistical Parametric Mapping (SPM8, v6313) and MATLAB R2014a (v8.3.0.532). Functional images were realigned to the mean image to reduce the effects of motion. The T1 structural image was then co-registered to the mean functional image. The realigned functional images were normalised to MNI (Montreal Neurological Institute) space using the unified segmentation approach with a voxel size of 2 × 2 × 2 mm3 (Ashburner and Friston, 2005) and then smoothed with an 8 mm FWHM (full width at half maximum) isotropic Gaussian filter. After pre-processing, graphical plots of estimated time series of translations and rotations were carefully inspected for excessive motion in each participant, defined as more than 3 mm translation and/or 3° rotation.

Using the CONN toolbox (v15; National Institutes of Health Blueprint for Neuroscience Research [https://www.nitrc.org/projects/conn]), functional data were temporally band-pass filtered (range: 0.008 - 0.09 Hz), and effects of motion and signals from white matter and cerebrospinal fluid were removed from the data using linear regression (Whitfield-Gabrieli and Nieto-Castanon, 2012).

**2.6 Resting-state functional connectivity analysis**

Based on a previous rs-fMRI study from our group (McCarthy et al., 2013), we examined functional connectivity within the default network, cognitive control network, affective network, and dorsal and ventral attention networks, as all networks are associated with cognitive functions severely disrupted in schizophrenia (**table 1**). Functional connectivity maps of Fisher-transformed correlation coefficients were computed by extracting the mean BOLD time-series from a seed region-of-interest (ROI) and correlating this time-series with the time series of all other voxels in the brain.

Seed regions-of-interest consisted of spheres of 5 mm radius centred on coordinates of interest from each network, with two seed regions extracted for each attention network (McCarthy et al., 2013). Coordinates of interest were derived from previous rs-fMRI studies (Fox et al., 2006; Sheline et al., 2010). Where coordinates were originally presented in Talaraich space, these were converted to MNI space using GingerALE 2.3 (‘Talairach to MNI (SPM)’ transform) (Eickhoff et al., 2009; Turkeltaub et al., 2012). ROIs were then created as masks using the Wake Forest University Pickatlas (Maldjian et al., 2003; Maldjian et al., 2004; Tzourio-Mazoyer et al., 2002). Networks and associated coordinates are presented in **table 2**. For each participant, functional connectivity maps were generated independently for left and right seeds, for each seed listed in **table 2**.

>> Table 2 <<

**2.7 Statistical analysis**

Functional connectivity maps for each seed region created by the CONN toolbox (BETA\_Subject\*.nii files) were compared between patients and controls using an independent t-test in SPM8 to examine regions showing altered connectivity in the five networks. Mean scan to scan translation and rotation were included in all second level models in SPM as covariates of no interest to further account for the effects of motion (**section 3.1**). Results were initially examined at a p<0.001 (uncorrected) level and clusters were considered statistically significant at p<0.01, family-wise error (FWE) corrected for multiple comparisons across the whole brain at the cluster level. This threshold was reduced from the standard threshold of p<0.05 as we analysed connectivity across five networks. Anatomical locations of peak coordinates of significant clusters were identified using the AllAreas\_v18\_MPM atlas within the Anatomy Toolbox in SPM8 (Eickhoff et al., 2005; Eickhoff et al., 2006; Eickhoff et al., 2007).

Within the patient group, we also examined effects of increasing positive and negative symptoms on functional connectivity with all seed regions showing a significant difference between patients and controls. To examine these effects, we used a multiple regression model in SPM8 with positive or negative symptom score as covariate of interest, and translation and rotation as covariates of no interest. Results of these tests were examined at a p<0.001 (uncorrected) level and clusters were considered statistically significant at a p<0.016 level, family-wise error (FWE) corrected for multiple comparisons across the whole brain at the cluster level (this threshold was reduced from the standard threshold of p<0.05 as we analysed connectivity across three networks where an initial difference was observed between patients and controls).

Once again, we used a multiple regression model in SPM8 with Reading the Mind in the Eyes score as covariate of interest, translation and rotation as covariates of no interest, and results of these tests were examined at a p<0.001 (uncorrected) level with clusters considered statistically significant at a p<0.016 level, family-wise error (FWE) corrected for multiple comparisons across the whole brain at the cluster level.

**3. Results**

**3.1 Participant demographics**

Age, mean scan to scan translation (in mm) and mean scan to scan rotation (in radians) were compared between schizophrenia patients and healthy controls using an independent t-test in SPSS (22.0.0). For each participant, translation and rotation values were calculated in MATLAB using the SPM realignment parameter data. Gender frequencies were compared between groups using a Pearson’s Chi-squared test in SPSS. There were no significant differences between groups on age, gender or translation (**table 3**). As the groups differed significantly in rotation, and due to the potentially confounding effects of motion in the estimation of resting-state functional connectivity, we included both translation and rotation as covariates of no interest across all second level analyses.

>> Table 3 <<

**3.2 Functional connectivity results**

Patients versus controls

Schizophrenia patients showed increased functional connectivity within the default mode network, and between this network and other brain regions compared to controls. Specifically, patients showed increased connectivity between the left precuneus and clusters incorporating (1) the left and right inferior frontal gyrus and (2) the medial prefrontal cortex (rectal gyrus and mid orbital gyrus) (p<0.01, FWE-corrected, tmax = 5.56, n = 52; see **table 4** and **figure 1**). Patients also showed increased connectivity between the right precuneus and the bilateral medial prefrontal cortex (mid orbital gyrus) (p<0.01, FWE-corrected, tmax = 4.30, n = 52; see **table 4** and **figure 1**) and between the left ACC and a cluster incorporating the cuneus and calcarine gyrus (p<0.01, FWE-corrected, tmax = 4.82, n = 52; see **table 4** and **figure 1**).

>> Table 4 <<

>> Figure 1 <<

In contrast, relative to controls, patients showed decreased functional connectivity between the left TPJ in the ventral attention network and a cluster incorporating the inferior temporal gyrus, inferior occipital gyrus and cerebellum compared to patients (p<0.01, FWE-corrected, tmax = 4.49, n = 52; see **table 5** and **figure 1**).

>> Table 5 <<

Positive symptom severity and default network connectivity

Within the patient group, increasing SAPS scores were associated with increased functional connectivity between the left ACC and a cluster incorporating the right precuneus and left posterior cingulate cortex (p<0.016, FWE-corrected, tmax = 5.38, n = 24; see **table 6** and **figure 2**).

>> Table 6 <<

>> Figure 2 <<

TOM and default network connectivity

Within the patient group, better Eyes task performance was associated with increased functional connectivity between the left precuneus and clusters incorporating the right middle cingulate and right inferior frontal gyrus (p<0.016, FWE-corrected, tmax = 6.87, n = 20; see **table 7** and **figure 2**) and between the left TPJ and clusters incorporating the right calcarine gyrus and right lingual gyrus (p<0.016, FWE-corrected, tmax = 6.04, n = 20; see **table 7** and **figure 2**). By comparison, lower scores were associated with increased functional connectivity between the left precuneus and clusters incorporating the right insula and left superior temporal gyrus (p<0.016, FWE-corrected, tmax = 6.75, n = 20; see **table 8** and **figure 2**). Given the correlation between the default network and positive symptoms, we also carried out a correlational analysis of TOM performance and positive symptom severity; no correlation was observed between these variables (r=-0.17; p=0.48).

>> Table 7 <<

>> Table 8 <<

**4. Discussion**

This study compared resting-state connectivity in schizophrenia patients and matched controls using previously defined networks. We confirmed previous evidence of default network hyper-connectivity in schizophrenia and association with positive symptom severity. As a novel finding, we report that default connectivity is predictive of TOM performance in schizophrenia.

Brain regions comprising the default mode network, including the medial prefrontal cortex and precuneus, show greater metabolic activity during rest, and play an important role in mind-wandering, autobiographical memory and TOM (Raichle et al., 2001; Mason et al., 2007; Buckner et al., 2008; Christoff et al., 2009). During many cognitive tasks, activity in this network is suppressed with increasing task difficulty, suggesting a redirection of processing resources from internally focussed attention towards the task at hand (Mckiernan et al., 2003). Weaker suppression of the default network is thus associated with poorer cognitive function, including poorer memory and attention (Daselaar et al., 2004; Weissman et al., 2006).

In schizophrenia, increased activity, functional connectivity and spatial extent of the default network has been repeatedly observed, with increasing connectivity and spatial extent also associated with increased positive symptom severity (Whitfield-Gabrieli et al., 2008; Garrity et al., 2008; Zhou et al., 2007). Our findings of increased connectivity between the precuneus and medial prefrontal cortex in patients relative to controls, and increased ACC - precuneus connectivity with increasing positive symptoms are consistent with previous findings.

The main novelty of our study is our observation of an association between increasing TOM performance (based on the Eyes test) and both increased and decreased functional connectivity of the left precuneus within the patient group. Specifically, patients who performed better at the task showed increased connectivity between the left precuneus and the prefrontal cortex, and decreased connectivity between the left precuneus and superior temporal gyrus and insula. As well as forming part of the default network, previous anatomical likelihood estimation meta-analysis has shown that the left precuneus is activated during TOM tasks across multiple studies (Spreng et al., 2009). Our finding that altered connectivity of this region is further associated with variation in TOM task performance in patients highlights the importance of this region for understanding and treating TOM deficits in schizophrenia.

The TPJ plays diverse roles in reorienting attention to salient stimuli in the environment, understanding speech, and reasoning about the thoughts of others (Van Overwalle, 2009), and part of the TPJ also forms part of the default network (Spreng et al., 2009). In addition to the default network in general, altered function of the left TPJ has previously been observed in schizophrenia and associated with auditory hallucinations (Vercammen et al., 2010), suggesting that this node of the default network in particular is important to TOM performance.

Whether the association between altered default network connectivity and TOM performance is specific to TOM, or is relevant to other aspects of social and general cognition was not directly assessed by this study. However, in a sample overlapping with the present sample, we recently showed that patients fail to deactivate an overlapping region of the medial prefrontal cortex while watching video clips of facial expressions (Mothersill et al., 2014a), and failure to deactivate the medial prefrontal cortex during other cognitive tasks (e.g. working memory performance) has also been reported in multiple schizophrenia studies (Meyer-Lindenberg et al., 2001; Pomarol-Clotet et al., 2008). Hyper-activity and hyper-connectivity of this network has also been associated with poorer working memory performance (Whitfield-Gabrieli et al., 2009).

Thus, hyper-connectivity and hyper-activity of the default network may play a key role in the cognitive deficits observed in schizophrenia and may provide an important treatment target. Consistent with this view, schizophrenia patients who undergo cognitive remediation training show decreased resting default network activation following training, and this change represents a normalisation towards the pattern seen in healthy controls in the same study (Penadés et al., 2013).

In conclusion, this study confirms previous evidence of default hyper-connectivity in schizophrenia and association with positive symptoms, and extends previous findings by demonstrating a novel association between default connectivity and TOM. Determining the extent to which genetic risk, environmental risk, and new treatments impact upon default connectivity, and how such effects may impact TOM and symptom severity, will be an important future direction.

**5. References**

Aleman, A., Kahn, R.S., 2005. Strange feelings: do amygdala abnormalities dysregulate the emotional brain in schizophrenia? Progress in neurobiology 77(5), 283-298.

Andreasen, N.C., 1983. Scale for the assessment of negative symptoms. University of Iowa, Iowa City.

Andreasen, N.C., 1984. Scale for the assessment of positive symptoms. Iowa City: University of Iowa.

Ashburner, J., Friston, K.J., 2005. Unified segmentation. Neuroimage 26(3), 839-851.

Baron-Cohen, S., Ring, H.A., Wheelwright, S., Bullmore, E.T., Brammer, M.J., Simmons, A., Williams, S.C.R., 1999. Social intelligence in the normal and autistic brain: an fMRI study. European Journal of Neuroscience 11(6), 1891-1898.

Baron‐Cohen, S., Wheelwright, S., Hill, J., Raste, Y., Plumb, I., 2001. The “Reading the mind in the eyes” test revised version: A study with normal adults, and adults with asperger syndrome or high‐functioning autism. Journal of Child Psychology and Psychiatry 42(2), 241-251.

Bora, E., Yucel, M., Pantelis, C., 2009. Theory of mind impairment in schizophrenia: meta-analysis. Schizophrenia research 109(1), 1-9.

Brüne, M., Abdel-Hamid, M., Lehmkämper, C., Sonntag, C., 2007. Mental state attribution, neurocognitive functioning, and psychopathology: what predicts poor social competence in schizophrenia best? Schizophrenia research 92(1-3), 151-159.

Buckner, R.L., Andrews‐Hanna, J.R., Schacter, D.L., 2008. The brain's default network. Annals of the New York Academy of Sciences 1124(1), 1-38.

Christoff, K., Gordon, A.M., Smallwood, J., Smith, R., Schooler, J.W., 2009. Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. Proceedings of the National Academy of Sciences 106(21), 8719-8724.

Daselaar, S., Prince, S., Cabeza, R., 2004. When less means more: deactivations during encoding that predict subsequent memory. Neuroimage 23(3), 921-927.

Eickhoff, S.B., Heim, S., Zilles, K., Amunts, K., 2006. Testing anatomically specified hypotheses in functional imaging using cytoarchitectonic maps. Neuroimage 32(2), 570-582.

Eickhoff, S.B., Laird, A.R., Grefkes, C., Wang, L.E., Zilles, K., Fox, P.T., 2009. Coordinate‐based activation likelihood estimation meta‐analysis of neuroimaging data: A random‐effects approach based on empirical estimates of spatial uncertainty. Human brain mapping 30(9), 2907-2926.

Eickhoff, S.B., Paus, T., Caspers, S., Grosbras, M.-H., Evans, A.C., Zilles, K., Amunts, K., 2007. Assignment of functional activations to probabilistic cytoarchitectonic areas revisited. Neuroimage 36(3), 511-521.

Eickhoff, S.B., Stephan, K.E., Mohlberg, H., Grefkes, C., Fink, G.R., Amunts, K., Zilles, K., 2005. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. Neuroimage 25(4), 1325-1335.

Fox, M.D., Corbetta, M., Snyder, A.Z., Vincent, J.L., Raichle, M.E., 2006. Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. Proceedings of the National Academy of Sciences 103(26), 10046-10051.

Garrity, A., Pearlson, G., McKiernan, K., Lloyd, D., Kiehl, K., Calhoun, V., 2007. Aberrant “default mode” functional connectivity in schizophrenia. American Journal of Psychiatry 164(3), 450-457.

Glahn, D.C., Ragland, J.D., Abramoff, A., Barrett, J., Laird, A.R., Bearden, C.E., Velligan, D.I., 2005. Beyond hypofrontality: A quantitative meta‐analysis of functional neuroimaging studies of working memory in schizophrenia. Human brain mapping 25(1), 60-69.

Keefe, R.S., Harvey, P.D., 2012. Cognitive impairment in schizophrenia, Novel antischizophrenia treatments. Springer, pp. 11-37.

Lee, J., Park, S., 2005. Working memory impairments in schizophrenia: a meta-analysis. Journal of abnormal psychology 114(4), 599.

Lewandowski, K.E., Cohen, B.M., Keshavan, M.S., Öngür, D., 2011. Relationship of neurocognitive deficits to diagnosis and symptoms across affective and non-affective psychoses. Schizophrenia research 133(1), 212-217.

Maldjian, J.A., Laurienti, P.J., Burdette, J.H., 2004. Precentral gyrus discrepancy in electronic versions of the Talairach atlas. Neuroimage 21(1), 450-455.

Maldjian, J.A., Laurienti, P.J., Kraft, R.A., Burdette, J.H., 2003. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage 19(3), 1233-1239.

Mason, M.F., Norton, M.I., Van Horn, J.D., Wegner, D.M., Grafton, S.T., Macrae, C.N., 2007. Wandering minds: the default network and stimulus-independent thought. Science 315(5810), 393-395.

McCarthy, H., Skokauskas, N., Mulligan, A., Donohoe, G., Mullins, D., Kelly, J., Johnson, K., Fagan, A., Gill, M., Meaney, J., Frodl, T., 2013. Attention network hypoconnectivity with default and affective network hyperconnectivity in adults diagnosed with attention-deficit/hyperactivity disorder in childhood. JAMA psychiatry 70(12), 1329-1337.

McGurk, S.R., Twamley, E.W., Sitzer, D.I., McHugo, G.J., Mueser, K.T., 2007. A meta-analysis of cognitive remediation in schizophrenia. The American journal of psychiatry 164(12), 1791-1802.

McKiernan, K.A., Kaufman, J.N., Kucera-Thompson, J., Binder, J.R., 2003. A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging. Journal of cognitive neuroscience 15(3), 394-408.

Meyer-Lindenberg, A., 2009. Neural connectivity as an intermediate phenotype: brain networks under genetic control. Hum Brain Mapp 30(7), 1938-1946.

Meyer-Lindenberg, A., Poline, J.B., Kohn, P.D., Holt, J.L., Egan, M.F., Weinberger, D.R., Berman, K.F., 2001. Evidence for abnormal cortical functional connectivity during working memory in schizophrenia. Am J Psychiatry 158(11), 1809-1817.

Mothersill, O., Morris, D.W., Kelly, S., Rose, E.J., Bokde, A., Reilly, R., Gill, M., Corvin, A.P., Donohoe, G., 2014a. Altered medial prefrontal activity during dynamic face processing in schizophrenia spectrum patients. Schizophrenia research 157(1-3), 225-230.

Mothersill, O., Morris, D.W., Kelly, S., Rose, E.J., Fahey, C., O'Brien, C., Lyne, R., Reilly, R., Gill, M., Corvin, A.P., Donohoe, G., 2014b. Effects of MIR137 on fronto-amygdala functional connectivity. Neuroimage 90, 189-195.

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(1), 29-39.

Nuechterlein, K.H., Green, M.F., Calkins, M.E., Greenwood, T.A., Gur, R.E., Gur, R.C., Lazzeroni, L.C., Light, G.A., Radant, A.D., Seidman, L.J., 2015. Attention/vigilance in schizophrenia: Performance results from a large multi-site study of the Consortium on the Genetics of Schizophrenia (COGS). Schizophrenia research 163(1), 38-46.

Penadés, R., Pujol, N., Catalán, R., Massana, G., Rametti, G., García-Rizo, C., Bargalló, N., Gastó, C., Bernardo, M., Junqué, C., 2013. Brain Effects of Cognitive Remediation Therapy in Schizophrenia: A Structural and Functional Neuroimaging Study. Biological psychiatry 73(1), 1015-1023.

Pezawas, L., Meyer-Lindenberg, A., Drabant, E.M., Verchinski, B.A., Munoz, K.E., Kolachana, B.S., Egan, M.F., Mattay, V.S., Hariri, A.R., Weinberger, D.R., 2005. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nat Neurosci 8(6), 828-834.

Pomarol-Clotet, E., Salvador, R., Sarro, S., Gomar, J., Vila, F., Martinez, A., Guerrero, A., Ortiz-Gil, J., Sans-Sansa, B., Capdevila, A., 2008. Failure to deactivate in the prefrontal cortex in schizophrenia: dysfunction of the default mode network? Psychological medicine 38(08), 1185-1193.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. Proceedings of the National Academy of Sciences 98(2), 676-682.

Roncone, R., Falloon, I.R., Mazza, M., de Risio, A., Pollice, R., Necozione, S., Morosini, P., Casacchia, M., 2002. Is theory of mind in schizophrenia more strongly associated with clinical and social functioning than with neurocognitive deficits? Psychopathology 35(5), 280-288.

Schurz, M., Radua, J., Aichorn, M., Richlan, F., Perner, J., 2014. Factionating theory of mind: A meta-analysis of functional brain imaging studies. Neuroscience and Biobehavioral Reviews 42, 9-34.

Sheline, Y.I., Price, J.L., Yan, Z., Mintun, M.A., 2010. Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. Proceedings of the National Academy of Sciences 107(24), 11020-11025.

Spreng, R.N., Mar, R.A., Kim, A.S., 2009. The common neural basis of autobiographical memory, prospection, navigation, theory of mind, and the default mode: a quantitative meta-analysis. Journal of cognitive neuroscience 21(3), 489-510.

Stephan, K.E., Friston, K.J., Frith, C.D., 2009. Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. Schizophr Bull 35(3), 509-527.

Turkeltaub, P.E., Eickhoff, S.B., Laird, A.R., Fox, M., Wiener, M., Fox, P., 2012. Minimizing within‐experiment and within‐group effects in activation likelihood estimation meta‐analyses. Human brain mapping 33(1), 1-13.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15(1), 273-289.

Van Overwalle, F., 2009. Social cognition and the brain: A meta‐analysis. Human brain mapping 30(3), 829-858.

Vercammen, A., Knegtering, H., Liemburg, E.J., den Boer, J.A., Aleman, A., 2010. Functional connectivity of the temporo-parietal region in schizophrenia: effects of rTMS treatment of auditory hallucinations. Journal of Psychiatric Research 44(11), 725-731.

Weissman, D., Roberts, K., Visscher, K., Woldorff, M., 2006. The neural bases of momentary lapses in attention. Nature neuroscience 9(7), 971-978.

Whitfield-Gabrieli, S., Nieto-Castanon, A., 2012. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain connectivity 2(3), 125-141.

Whitfield-Gabrieli, S., Thermenos, H.W., Milanovic, S., Tsuang, M.T., Faraone, S.V., McCarley, R.W., Shenton, M.E., Green, A.I., Nieto-Castanon, A., LaViolette, P., 2009. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. Proceedings of the National Academy of Sciences 106(4), 1279-1284.

Zhou, Y., Liang, M., Tian, L., Wang, K., Hao, Y., Liu, H., Liu, Z., Jiang, T., 2007. Functional disintegration in paranoid schizophrenia using resting-state fMRI. Schizophrenia research 97(1), 194-205.

**Tables**

**Table 1:** Five networks examined in this study, prominent brain regions, proposed cognitive functions and relevance to schizophrenia

|  |  |  |  |
| --- | --- | --- | --- |
| **Resting-state network** | **Prominent brain regions** | **Proposed cognitive functions** | **Relevance to schizophrenia** |
| Default mode | Precuneus/posterior cingulate, medial prefrontal cortex, and temporo-parietal junction | Theory of mind; internally focussed tasks such as autobiographical memory | Theory of mind impairment is a core feature (Bora et al., 2009). |
| Cognitive control | Lateral prefrontal cortex, posterior parietal cortex | Executive function, including working memory | Working memory impairment is a core feature (Lee and Park, 2005). |
| Affective | Anterior cingulate cortex, amygdala | Emotion processing and regulation | Emotion processing deficits are a core feature (Aleman and Kahn, 2005) |
| Dorsal attention | Frontal eye field and intraparietal sulcus | Control of attention based on internal goals | Attentional deficits are a core feature (Keefe and Harvey, 2012; Nuechterlein et al., 2015) |
| Ventral attention | Temporo-parietal junction and ventral frontal cortex | Reorienting of attention to salient stimuli | Attentional deficits are a core feature (Keefe and Harvey, 2012; Nuechterlein et al., 2015) |

**Table 2:** Resting-state networks and associated seed coordinates in MNI space

|  |  |
| --- | --- |
| **Network** | **Seed coordinates (x y z)** |
| Default mode network (precuneus) | ±9 -60 25 |
| Cognitive control network (DLPFC) | ±40 33 24 |
| Affective network (ACC) | ±12 39 -11 |
| Dorsal attention network 1 (FEF) | ±28 -7 53 |
| Dorsal attention network 2 (IPS) | ±31 -55 55 |
| Ventral attention network 1 (TPJ) | ±59 -47 22 |
| Ventral attention network 2 (VFC) | ±41 21 -6 |

DLPFC = dorsolateral prefrontal cortex; ACC = anterior cingulate cortex; FEF = frontal eye fields; IPS = intraparietal sulcus; TPJ = temporo-parietal junction; VFC = ventral frontal cortex

**Table 3:** Participant demographics

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Gender (M:F) | Mean age (s.d.) | Mean translation (s.d.) (mm) | Mean rotation (s.d.) (radians) |
| Schizophrenia patients (n = 27) | 20:7 | 41.07 (10.56) | 0.070 (0.035) | <0.01 (<0.01) |
| Healthy controls (n = 25) | 17:8 | 37.40 (9.49) | 0.059 (0.028) | <0.01 (<0.01) |
| Statistic | χ2 = 0.233 | t = 1.316 | t = 1.278 | t = 3.240 |
| p-value | 0.629 | 0.194 | 0.207 | 0.002 |

s.d. = standard deviation; t-values were obtained from independent t-tests between the groups, χ2 value was obtained from Pearson’s Chi-squared test.

Mean Scale for the Assessment of Positive Symptoms score and s.d. (SAPS (Andreasen, 1984); rounded to two decimal places; data available for 24 of 27 patients) = 7.58 (12.28).

Mean Scale for the Assessment of Negative Symptoms score and s.d. (SANS (Andreasen, 1983); rounded to two decimal places; data available for 24 of 27 patients) = 13.33 (17.85).

Mean medication (Chlorpromazine equivalent in mg per day and s.d.; rounded to two decimal places; data available for 21 of 27 patients) = 356.57 (222.16).

**Table 4:** Clusters, including individual peaks, showing increased functional connectivity in schizophrenia patients relative to healthy controls, FWE-corrected across the whole brain at the cluster level

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Seed region** | **Cluster** | **Extent (voxels)** | **p value** | **Cluster peak** | **t-value** | **Z-value** | **Peak (MNI)** |
| Left precuneus | 1 | 261 | 0.008 | Inferior frontal gyrus  (pars orbitalis) | 5.56 | 4.86 | 40 36 -18 |
|  |  |  |  | Inferior frontal gyrus  (pars orbitalis) | 3.65 | 3.41 | 28 30 -14 |
|  | 2 | 323 | 0.002 | Inferior frontal gyrus  (pars orbitalis) | 4.65 | 4.21 | -46 28 -16 |
|  |  |  |  | Inferior frontal gyrus  (pars orbitalis) | 4.15 | 3.81 | -50 38 -14 |
|  |  |  |  | Inferior frontal gyrus  (pars orbitalis) | 3.85 | 3.58 | -32 32 -16 |
|  | 3 | 261 | 0.008 | Rectal gyrus | 4.27 | 3.91 | 10 34 -18 |
|  |  |  |  | Mid orbital gyrus | 4.27 | 3.91 | 4 38 -12 |
|  |  |  |  | Mid orbital gyrus | 4.11 | 3.79 | -4 40 -10 |
| Right precuneus | 1 | 345 | 0.002 | Mid orbital gyrus | 4.30 | 3.93 | -10 44 -10 |
|  |  |  |  | Mid orbital gyrus | 4.25 | 3.90 | 4 34 -12 |
|  |  |  |  | Mid orbital gyrus | 3.88 | 3.60 | 8 50 -12 |
| Left ACC\* | 1 | 436 | <0.001 | Cuneus | 4.82 | 4.33 | -10 -66 24 |
|  |  |  |  | Cuneus | 4.80 | 4.32 | -2 -70 24 |
|  |  |  |  | Calcarine gyrus | 3.71 | 3.46 | 0 -64 14 |

\*ACC = anterior cingulate cortex

**Table 5:** Clusters, including individual peaks, showing decreased functional connectivity in schizophrenia patients relative to healthy controls, FWE-corrected across the whole brain at the cluster level

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Seed region** | **Cluster** | **Extent (voxels)** | **p value** | **Cluster peak** | **t-value** | **Z-value** | **Peak (MNI)** |
| Left TPJ\* | 1 | 264 | 0.009 | Inferior temporal gyrus | 4.49 | 4.08 | -56 -52 -24 |
|  |  |  |  | Inferior occipital gyrus | 4.38 | 4.00 | -54 -66 -18 |
|  |  |  |  | Cerebellum | 3.97 | 3.67 | -46 -70 -22 |

\*TPJ = temporo-parietal junction

**Table 6:** Clusters, including individual peaks, showing increased functional connectivity in schizophrenia patients with increasing SAPS scores, FWE-corrected across the whole brain at the cluster level

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Seed region** | **Cluster** | **Extent (voxels)** | **p value** | **Cluster peak** | **t-value** | **Z-value** | **Peak (MNI)** |
| Left ACC\* | 1 | 398 | <0.001 | Precuneus | 5.38 | 4.18 | 2 -56 22 |
|  |  |  |  | Posterior cingulate | 4.70 | 3.81 | -4 -50 22 |

\*ACC = anterior cingulate cortex

**Table 7:** Clusters, including individual peaks, showing increased functional connectivity in schizophrenia patients with increasing Reading the Mind in the Eyes scores, FWE-corrected across the whole brain at the cluster level

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Seed region** | **Cluster** | **Extent (voxels)** | **p value** | **Cluster peak** | **t-value** | **Z-value** | **Peak (MNI)** |
| Left precuneus | 1 | 201 | 0.009 | Not found on any probability map | 6.87 | 4.62 | 26 -34 34 |
|  |  |  |  | Middle cingulate cortex | 5.36 | 4.00 | 12 -46 34 |
|  |  |  |  | Not found on any probability map | 4.67 | 3.65 | 24 -26 40 |
|  | 2 | 210 | 0.007 | Not assigned | 6.27 | 4.39 | 30 0 38 |
|  |  |  |  | Inferior frontal gyrus  (pars opercularis) | 4.76 | 3.70 | 44 16 30 |
|  |  |  |  | Inferior frontal gyrus  (pars opercularis) | 4.04 | 3.31 | 36 8 28 |
| Left TPJ\* | 1 | 574 | <0.001 | Calcarine gyrus | 6.04 | 4.30 | 12 -68 10 |
|  |  |  |  | Lingual gyrus | 5.36 | 4.00 | 18 -62 2 |
|  |  |  |  | Calcarine gyrus | 5.27 | 3.96 | -10 -84 4 |

\*TPJ = temporo-parietal junction

**Table 8:** Clusters, including individual peaks, showing decreased functional connectivity in schizophrenia patients with increasing Reading the Mind in the Eyes scores, FWE-corrected across the whole brain at the cluster level

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Seed region** | **Cluster** | **Extent (voxels)** | **p value** | **Cluster peak** | **t-value** | **Z-value** | **Peak (MNI)** |
| Left precuneus | 1 | 301 | 0.001 | Insula | 6.75 | 4.58 | 40 -12 -8 |
|  |  |  |  | Insula lobe | 5.86 | 4.22 | 40 -2 -8 |
|  |  |  |  | Not found on any probability map | 5.86 | 4.22 | 36 6 -8 |
|  | 2 | 487 | <0.001 | Superior temporal gyrus | 5.78 | 4.19 | -60 -30 20 |
|  |  |  |  | Not found on any probability map | 5.42 | 4.03 | -68 -24 16 |
|  |  |  |  | Superior temporal gyrus | 5.06 | 3.86 | -64 -36 14 |

**Figures**

**Figure 1:** Clusters showing altered resting functional connectivity in schizophrenia patients compared to healthy controls.

Bar-charts represent mean connectivity estimates extracted from the largest cluster showing a difference between patients and controls for each seed region; all clusters are significant at p<0.01, FWE-corrected across the whole brain at the cluster level; each 2D axial slice is labelled with an MNI-coordinate. Clusters were rendered on the ‘ch256’ brain template using MRIcroGL (http://www.mccauslandcenter.sc.edu/mricrogl/). Additional editing of figure (e.g. changing the size/resolution) was performed using MS Paint and Paint.NET v3.5.10.

**Figure 2:** Clusters showing altered resting functional connectivity in schizophrenia patients with increasing positive symptoms and Reading the Mind in the Eyes scores

Scatter plot points represent mean connectivity estimates extracted from the largest cluster showing an effect of SAPS or Eyes score for each seed region. Eyes = Reading the Mind in the Eyes score. Clusters are significant at p<0.016, FWE-corrected across the whole brain at the cluster level; each 2D axial slice is labelled with an MNI-coordinate. Clusters were rendered on the ‘ch256’ brain template using MRIcroGL (http://www.mccauslandcenter.sc.edu/mricrogl/). Additional editing of figure (e.g. changing the size/resolution) was performed using MS Paint and Paint.NET v3.5.10.