Impaired cortico-limbic functional connectivity in schizophrenia patients during emotion processing

Magali Comte, Xavier Y. Zendjidjian, Jennifer T. Coull, Aïda Cancel, Claire Boutet, Fabien C. Schneider, Thierry Sage, Pierre-Emmanuel Lazerges, Nematollah Jaafari, El Chérif Ibrahim, Jean-Michel Azorin, Olivier Blin, and Eric Fakra

1Timone Institute of Neuroscience, UMR 7289, CNRS and Aix-Marseille University, Marseille, France, 2Department of Psychiatry, La Conception University Hospital, Marseille, France, 3Cognitive Neurosciences Laboratory, UMR 7291, CNRS and Aix-Marseille University, Marseille, France, 4Department of Psychiatry, University Hospital of Saint-Etienne, Saint-Etienne, France, 5Inserm U1059, University of Lyon, Saint-Etienne, France, 6Neuroradiology Unit, University Hospital of Saint-Etienne, Saint-Etienne, France, 7Clinic of Mental Health, L’escala, Orpea-Clínica, Saint-Victoret, France, 8Department of Psychiatry, Sainte Marguerite University Hospital, Marseille, France, 9Intersector Clinical Psychiatric Research Unit, Psychobiology of Compulsive Disorders Team, Experimental and Clinical Neurosciences Laboratory, Henri Laborit Hospital, INSERM U 1084, University of Poitiers; Experimental and Clinical Neurosciences Laboratory, CIC INSERM U 802, Poitiers, France, 10CRN2M-UMR7286, CNRS and Aix-Marseille University, Marseille, France, 11FondaMental Fundation, Fundation of Research and Mental Health Care, Créteil, France, and 12Unit for Clinical Pharmacology and Therapeutic Evaluation (CIC-UPCET), Timone Hospital, Public Assistance for Marseille Hospitals (APHM), Marseille, France

Correspondence should be addressed to Pr. Eric Fakra, CHU Saint-Etienne, Pôle Universitaire de Psychiatrie, 5 Chemin de la Marendière, 42055 Saint-priest-en-Jarez Cedex 2, France. E-mail: Eric.Fakra@chu-st-etienne.fr

Abstract

Functional dysconnection is increasingly recognized as a core pathological feature in schizophrenia. Aberrant interactions between regions of the cortico-limbic circuit may underpin the abnormal emotional processing associated with this illness. We used a functional magnetic resonance imaging paradigm designed to dissociate the various components of the cortico-limbic circuit (i.e. a ventral automatic circuit that is intertwined with a dorsal cognitive circuit), to explore bottom-up appraisal as well as top-down control during emotion processing. In schizophrenia patients compared with healthy controls, bottom-up processes were associated with reduced interaction between the amygdala and both the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex. Contrariwise, top-down control processes led to stronger connectivity between the ventral affective and the dorsal cognitive circuits, i.e. heightened interactions between the ventral ACC and the dorsolateral prefrontal cortex as well as between dorsal and ventral ACC. These findings offer a comprehensive view of the cortico-limbic dysfunction in schizophrenia. They confirm previous results of impaired propagation of information between the amygdala and the prefrontal cortex and suggest a defective functional segregation in the dorsal cognitive part of the cortico-limbic circuit.

Received: 6 November 2016; Revised: 8 June 2017; Accepted: 19 June 2017
Key words: affect; functional magnetic resonance imaging; amygdala; anterior cingulate cortex; prefrontal cortex; schizophrenia

Introduction

Emotional disturbances are critical features of schizophrenia with significant consequences for clinical trajectory and functional outcome (Yung and McGorry, 1996; Hafner et al., 2003; Kee et al., 2003). Research on healthy individuals suggests that emotional processing is mediated through reciprocal interaction of a ventral and a dorsal system, which define the cortico-limbic circuit. Schematically, the ventral system is centered in the limbic regions, particularly the amygdala, and is involved in bottom-up appraisal of emotional information and subsequent production of the affective state. The dorsal system, which includes the dorsal regions of the prefrontal cortex (PFC) and the anterior cingulate cortex (ACC), enables top-down regulation of emotional responses (Phillips et al., 2003, 2008).

Neuroimaging studies of emotional processing in schizophrenia have extensively focused on the amygdala, given its cardinal role in affective processing. There is, however, a disparity in the results reported to date. Numerous studies show underrecruitment of the amygdala in schizophrenia patients (Gur et al., 2002; Paradiso et al., 2003; Takahashi et al., 2004; Seiferth et al., 2009), while others demonstrate intact or even overrecruitment of the amygdala (Kosaka et al., 2002; Taylor et al., 2005; Holt et al., 2006; Hall et al., 2008). Recent meta-analyses report a modest degree of amygdala underrecruitment in schizophrenia patients as compared with healthy controls (Anticevic et al., 2012; Taylor et al., 2012). Yet between-group differences in amygdala activity are strongly determined by methodological variables (e.g. the use of neutral stimuli as control condition) (Hall et al., 2008; Blasi et al., 2009; Salgado-Pineda et al., 2010; Anticevic et al., 2012; Taylor et al., 2012). It remains therefore difficult to reach firm conclusions. Similarly, an extensive literature describes dysfunctional engagement of PFC in schizophrenia, particularly in the dorsolateral PFC (DLPFC) and the ACC, during tasks of executive function (Weinberger et al., 1986; Barch et al., 2003; Kerns et al., 2005). Importantly, control processes mediated by prefrontal and cingulate cortices also contribute to emotional processing (Ochsner and Gross, 2005), notably through the interpretation and regulation of emotions (Phan et al., 2002; Delgado et al., 2008; Goldin et al., 2008). Although prefrontal recruitment has been poorly explored in the context of emotional tasks, some studies have shown abnormal engagement of DLPFC as well as ACC in schizophrenia or psychosis proneness during tasks requiring cognitive reappraisal or inhibition of emotional distractors (Park et al., 2008; Dichter et al., 2010; Modinos et al., 2010; Anticevic et al., 2011; Morris et al., 2012; van der Meer et al., 2014).

Rather than considering solely the blood oxygen level-dependent (BOLD) activation of restricted brain regions, the exploration of connectivity in brain circuits may be more informative. The disconnection hypothesis in schizophrenia has become increasingly influential (Weinberger et al., 1992; Friston and Frith, 1995). It relies on converging evidence of widely distributed abnormalities in structural and functional connectivity (Weinberger et al., 1992; Friston and Frith, 1995; Stephan et al., 2006; Pettersson-Yeo et al., 2011; Buckholtz and Meyer-Lindenberg, 2012). This theory proposes that abnormal integration between distinct brain regions underlies the impairments found in schizophrenia (Friston and Frith, 1995). Accordingly, the aberrant emotional responses observed in schizophrenia may result from impaired connectivity between cortico-limbic regions that support emotional processing. Connectivity studies in schizophrenia have mainly focused on amygdala interactions and principally shown that patients have absent or decreased amygdala functional connectivity with PFC during emotional facial processing (Das et al., 2007; Falera et al., 2008; Satterthwaite et al., 2010), negative affective interference (Anticevic et al., 2012) and at rest (Anticevic et al., 2014; Liu et al., 2014). There is also some evidence to suggest disturbed integration within prefrontal regions in patients during cognitive tasks (Kryiakopoulos et al., 2012; Sambataro et al., 2012). However, the functional connectivity of dorsal cognitive regions in schizophrenia patients has yet to be addressed within an emotional context. Furthermore, by focusing solely on ‘bottom-up’ or ‘top-down’ mechanisms, the results of previous studies make it difficult to draw definitive assumptions about the respective involvement of appraisal and control systems in the emotional disturbances observed in schizophrenia. In this study, we explored changes in functional connectivity in schizophrenia patients during an emotional task purposely designed to dissociate the various components of the cortico-limbic circuit, that is, the dorsal cognitive circuit (dorsal ACC-DLPFC) and the ventral automatic circuit (ventral ACC-amygdala). More specifically, the task varied according to three parameters that differentially indexed processes of appraisal and regulation: emotional valence (positive or negative), emotional congruency (same or opposite emotional stimulus content) and allocation of attention (low or high attentional load) (Comte et al., 2014).

Materials and methods

Participants

Twenty-eight patients with schizophrenia and 33 demographically matched healthy volunteers completed the study. All patients fulfilled diagnostic and statistical manual of mental disorders (DSM)-IV-repetition time (TR) criteria for schizophrenia (American Psychiatric Association, 2000) and were stabilized by antipsychotic monotherapy with Aripiprazole or Risperidone for at least 6 weeks prior to the study. Healthy controls were matched to patients on gender, age and education. The non-patient version of the Structured Clinical Interview for DSM-IV (First et al., 2002) was used to ensure the absence of any psychiatric disorder or psychiatric history in control participants. Individuals were excluded from both groups if any of the following were present: magnetic resonance imaging (MRI) contraindication; history of head trauma or neurological disorder; concomitant major medical disorder or drug abuse. All participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). This study was conducted in accordance with the principles of the declaration of Helsinki. Approval was obtained from the local ethics committee (Comité de protection des personnes, Marseille). Each participant gave informed written consent before entering the study.

Data from nine participants were removed because of excessive head motion, anomalies detected on anatomical scans or visible artifacts in functional images. Thus, the final analyses included data from 26 patients and 26 healthy controls (Table 1).

Experimental paradigm

In the experimental task [variable attention and congruency task (VAAT), Comte et al., 2014], participants were presented with images composed of two parts. The central part of the
image displayed photographs of faces expressing positive emotion (joy) or negative emotion (fear, disgust or anger), from the NimStim Face stimulus set (Tottenham et al., 2008). Subjects were asked to focus on the part of the image framed in green (either the central face or the peripheral scene) and determine its emotional content (pleasant vs unpleasant) by pressing the corresponding key.

The task (VAAT) consisted of $2 \times 2 \times 2$ conditions varying according to emotional valence (positive or negative), emotional congruency (same or different emotional content in the face and the scene) and attentional load [attention focused on the face (low attention) vs on the scene (high attention)]. The VAAT had a mixed event-related/block design, comprising four sessions of 6 min 8 s each. The sessions were divided in 16 blocks that each lasted 20.4 s. The blocks began by an instruction panel (displayed during 1400 ms) specifying which part of the image the participant had to focus on during the block, followed by four experimental trials, each lasting 3000 ms, during which time subjects provided their response. The valence parameter varied from trial to trial whereas the congruency and attention parameters varied from block to block. The interstimulus interval (ISI) and interblock interval (IBI) were randomly jittered ranging from 1 to 1.8 s for the ISI and from 1.2 to 2 s for the IBI, with a respective mean of 1.4 and 1.6 s. Block order was randomized within sessions, and the order of the sessions was counterbalanced across subjects.

### Behavioral data analysis

Behavioral data [reaction time (RT) and accuracy] were analyzed using statistical package for the social sciences (SPSS) (v18.0). Effects of diagnostic and task conditions on participants’ performance were assessed by entering subjects’ mean RT and accuracy for each condition into a mixed model analysis of variance (ANOVA) with one between-subject factor (schizophrenia patients vs healthy controls) and three within-subject factors (emotional valence, emotional congruency and attentional load). In case of significant effects, Bonferroni corrections were applied in post hoc analyses to correct for multiple comparisons.

### MRI acquisition

Data were acquired on a 3-T MEDSPEC 30/80 AVANCE imager (Bruker). After an initial localizing scan, functional data were acquired using a T2*-weighted gradient-echo planar imaging sequence ($TR = 5000 \text{ ms}; \text{echo time} (TE) = 30 \text{ ms}; \text{field-of-view (FOV)} = 192 \times 192 \text{ mm}; 64 \times 64 \text{ matrix; flip angle} 84.8^\circ$; voxel size $3 \times 3 \times 3 \text{ mm}^3$). Four functional runs of 45 interleaved axial slices were acquired along the anterior–posterior commissure plane with a continuous slice thickness of 3 mm. Following the functional MRI (fMRI) scans, high-resolution anatomical images were acquired for the purpose of anatomical identification with a sagittal T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) sequence ($TR = 9.4 \text{ ms}; TE = 4.42 \text{ ms}; \text{inversion time} (TI) = 800 \text{ ms}; 256 \times 256 \times 180 \text{ matrix; flip angle} 30^\circ$; voxel size $1 \times 1 \times 1 \text{ mm}^3$).

### fMRI data analysis

All data were analyzed using SPM8 software (Wellcome department of Cognitive Neurobiology, University College London; http://www.fil.ion.ucl.ac.uk/spm/software/spm8). We performed standard preprocessing procedures, including slice timing correction, motion correction, coregistration of anatomical images to the functional images, normalization into the Montreal Neurological Institute space and smoothing with a 6 mm Gaussian kernel. Realignment plots were examined to ensure the absence of excessive movements during the scan. Data were discarded from further analysis if movements in any axis were superior to 3 mm and/or 2 °.

The preprocessed functional images were analyzed using an event-related approach. Hemodynamic responses were modeled using a canonical function and convolved with the onsets and durations of each condition to form the general linear model. Six movement parameters were included in the analysis as regressors of no interest. A 128 s high-pass filter was applied to the data to remove low-frequency noise. First-level contrast images were calculated to estimate BOLD signal changes due to variations in: emotional valence (negative vs positive valence conditions), emotional congruency (incongruent vs congruent conditions) and attentional load [attention to the scene (high) vs attention to the face (low)]. The first-level contrast images were then entered into a second-level two-sample t-test with a random effects statistical model to examine between-group effects. We used a region of interest (ROI) approach focusing on areas previously implicated in emotion processing: the amygdala, ACC and DLPFC. The ROIs were anatomically defined using the Automated Anatomical Labeling software implemented in the Wake Forest University School of Medicine PickAtlas (WFU PickAtlas (Maldjian et al., 2003). Results were examined at $P < 0.001$ voxel-wise (uncorrected for multiple comparisons), and clusters were considered significant at $P < 0.05$ family-wise error (FWE) corrected at the cluster level. Finally, we also performed exploratory whole-brain analyses, with a threshold of $P < 0.001$ (uncorrected) and a 10 voxel spatial extent.

### Functional connectivity analyses

We used a generalized form of psychophysiological interaction (gPPI, http://brainmap.wisc.edu/PPI) (McLaren et al., 2012) to...
assess context-dependent variations in functional connectivity between the ROI. gPPI can model all task conditions simultaneously resulting in a better model fit compared with traditional PPI analyses. We conducted three separate gPPI analyses using the three ROI as seed regions to examine the differences in their functional interactions according to either the negative > positive contrast (for the amygdala), incongruent > congruent contrast (for the ACC) and high attention > low attention contrast (for the DLPFC). For each subject, the seed masks were created using a 5 mm radius sphere (3 mm for the amygdala) around the coordinates of the subject-specific local maxima in the ROI that were within 15 mm (10 mm for the amygdala) of the between-group difference maxima or, in absence of significant group difference, of the healthy group maxima and within the same anatomical mask, as defined by the PickAtlas toolbox (Maldjian et al., 2003). Within each seed region, the time series of the first eigenvector of the BOLD signal were temporally filtered, mean corrected and deconvolved to generate the physiological variable. PPI terms were computed as the cross product of the physiological variable and each task regressor (negative valence, positive valence, congruent, incongruent, low attentional load and high attentional load). Finally, the physiological variable of the seed region, the psychological regressors and PPI variables were entered as regressors in a first-level general linear model (GLM). The six movement parameters were also included in the model as nuisance variables.

The individual contrast images were then entered into second-level analyses using two-sample t-tests to assess between-group effects on functional connectivity. Given the subtle nature of brain activity during emotion processing, the use of a priori defined regions, and the general tendency of PPI analyses to lack power and generate a high proportion of false negatives (O’Reilly et al., 2012), group differences were assessed at a combined statistical threshold of P < 0.005 voxel-wise with a 10 voxel extent threshold. This approach provides a reasonable balance with respect to types I and II error concerns (Lieberman and Cunningham, 2009) and is consistent with earlier studies on emotional processing in psychiatric populations (Foland et al., 2008; Monk et al., 2008; Townsend et al., 2013).

Finally, to assess any associations between functional brain imaging data and either severity of symptoms or treatment, additional analyses were conducted in patients. Doses of antipsychotic medication were converted to chlorpromazine equivalence (Woods, 2003). Using the MARSBAR toolbox (Brett et al., 2002), we extracted for each patient the mean activity and connectivity beta values from the significant clusters obtained in between-group analyses. We carried out correlation analyses between BOLD activation and functional connectivity data and chlorpromazine equivalent, as well as each dimension of the Positive and Negative Syndrome Scale (negative, positive, cognitive, excitement and depression) (Lindenmayer et al., 1995). Bonferroni corrections were applied to correct for multiple comparisons.

**Results**

**Behavioral data**

The mixed model ANOVA revealed a significant main effect of group (F 1,50 = 4.54, P = 0.038) on RT, suggesting that schizophrenia patients were generally slower than healthy controls. Results also showed main effects of congruency (F 1,50 = 11.45, P = 0.001) and attention (F 1,50 = 188.35, P < 0.001). There was no significant main effect of valence on RT. There was a significant interaction between group and congruency (F 1,50 = 5.40, P = 0.024). Post hoc t-tests revealed that the slowing induced by incongruency (RTs for incongruent stimuli minus RTs for congruent stimuli) was amplified in patients compared with controls (t 50 = 2.32, P = 0.024). There was no significant group × attention interaction (Supplementary Figure S1).

Participants’ accuracy was high, with a mean value of 92.3% (s.d. = 1) for healthy controls and 85.5% (s.d. = 2.1) for schizophrenia patients. There was a main effect of group (F 1,50 = 8.31, P = 0.006), indicating that patients were generally less accurate in performing the task. The mixed model ANOVA also revealed main effects of congruency (F 1,50 = 14.40, P < 0.001). There was no significant main effect of valence or attention on accuracy. There was a significant interaction between group and congruency (F 1,50 = 4.46, P = 0.040). Post hoc t-tests suggested that the decrease in accuracy as a function of congruency (% correct for incongruent stimuli minus % correct for congruent stimuli) was greater for patients compared with controls (t 50 = 2.11, P = 0.040); however, this result did not survive Bonferroni correction for multiple comparisons (Supplementary Figure S1).

Because behavioral data suggest that the task may have been more difficult for schizophrenia patients than healthy controls, all imaging analyses reported below were carried out with subjects’ between-task mean RT and accuracy differences entered as covariates, thus ensuring that effects of task difficulty would not confound interpretation of the fMRI data (Price and Friston, 1999; Callicott et al., 2000).

**fMRI data**

**Regional brain activation.** For the valence contrast (negative vs positive stimuli), t-test analysis revealed no significant group differences in amygdala activity. Likewise, the comparison between incongruent and congruent conditions revealed no significant group differences in BOLD signal within the ACC that survived cluster-wise FWE correction for multiple comparisons. Finally, when comparing high with low attentional load (i.e. focusing on the scene rather than the face), patients demonstrated decreased activity relative to controls within the right DLPFC [x, y, z = 52, 24, 28; k = 29; T = 3.5; P (FWE cluster-wise) = 0.043], indicating weaker recruitment of this region in patients in response to higher attentional demands. Results obtained from whole-brain analyses are displayed in Supplementary Table S1.

**Functional connectivity: gPPI.** In response to negative valence compared with positive valence stimuli, gPPI analyses revealed that schizophrenia patients, relative to healthy controls, exhibited significant weaker task-related increase in functional coupling between the amygdala seed region and both dorsal ACC (x, y, z = 2, 14, 28; k = 35; T = 3.73; P < 0.005) and ventral ACC (x, y, z = 8, 34, −10; k = 16; T = 3.54; P < 0.005), as well as left DLPFC (x, y, z = −46, 8, 22; k = 30; T = 3.45; P < 0.005). In response to incongruent vs congruent trials, patients compared with controls showed stronger task-related functional connectivity between the dorsal ACC seed region and more ventral parts of the ACC (x, y, z = −12, 44, 14; k = 37; T = 4.22; P < 0.005; x, y, z = 6, 46, 16; k = 23; T = 3.33; P < 0.005; and x, y, z = 42, −8; k = 12; T = 3.29; P < 0.005). Finally, as a result of increased attentional load, patients compared with controls, exhibited increased task-related functional connectivity between the DLPFC seed region and ventral ACC (x, y, z = 2, 26, 14; k = 29; T = 3.14; P < 0.005) (Figure 1).

Furthermore, there was a significant negative correlation between DLPFC activity in high attentional condition compared...
with low attentional condition and antipsychotic dosage ($r = -0.504$, $P = 0.009$). No other correlation survived Bonferroni correction for multiple comparisons.

**Discussion**

This study explored variations in functional connectivity underlying bottom-up appraisal and top-down regulation mechanisms during emotion processing in schizophrenia patients. For this purpose, we independently manipulated three experimental parameters: emotional valence assessed bottom-up processing, whereas congruency and allocation of attention evaluated top-down modulation. Regarding bottom-up appraisal processing, schizophrenia patients relative to healthy controls demonstrated reduced task-related functional interaction between the amygdala seed region and prefrontal cortical regions (dorsal and ventral ACC as well as left DLPFC). Concerning top-down processes, patients showed a broad pattern of increased task-related functional connectivity in the dorsal component of the cortico-limbic system. More precisely, this pattern was characterized by increased task-related coupling between the dorsal ACC seed region and ventral ACC as well as enhanced task-related coupling between the DLPFC seed region and ventral ACC.

**Bottom-up processes**

Our findings reveal reduced task-related functional interaction (i.e. weaker increase in connectivity in response to negative compared with positive stimuli) between the amygdala and both ACC and DLPFC. This result confirms previous literature reporting decreased or absent connectivity between the

---

**Fig. 1. Functional connectivity analyses.** Upper panel (I): voxels in ACC (B) and in left DLPFC (C) that show lower connectivity with the right amygdala (A) in schizophrenia patients compared with healthy controls. (D) Schematic representation of between-group differences in amygdala functional connectivity as a function of valence; the blue arrows represent decreased connectivity in patients compared with controls. Middle panel (II): voxels in the ventral ACC (E) that show stronger connectivity with the dorsal ACC (F) in patients compared with controls during emotional conflict. (G) Schematic representation of between-group differences in dorsal ACC functional connectivity as a function of conflict; the red arrows represent increased connectivity in patients compared with controls. Bottom panel (III): voxels in the ventral ACC (H) that show stronger connectivity with the right DLPFC (I) in patients compared with controls during high attentional load conditions. (J) Schematic representation of between-group differences in DLPFC functional connectivity as a function of attention. Results are displayed on a single subject’s anatomical slices, at $P < 0.005$ (uncorrected).
amygdala and the PFC during emotional tasks (Das et al., 2007; Fakra et al., 2008; Satterthwaite et al., 2010; Anticevic et al., 2012) or at rest (Anticevic et al., 2014; Liu et al., 2014). The amygdala is believed to be involved in early/automatic processing of the emotional salience of sensory stimuli (Davis and Whalen, 2001; Phillips et al., 2003), and to signal the occurrence of biologically relevant sensory stimuli in preparation for an appropriate response (LeDoux, 2000). In so doing, the amygdala mediates the privileged access of emotional information (particularly that related to fear) to attentional systems, through a bottom-up influence on higher-order executive control regions (Armony and LeDoux, 1997; Whalen et al., 1998; Phelps, 2006). Conversely, the prefrontal and cingulate cortices are regions strongly related to the evaluative aspects of emotional processing (Hariri et al., 2003), such as awareness and interpretation of emotional stimuli (Lane et al., 1997; Davidson and Irwin, 1999; Phan et al., 2002; Ochsner and Gross, 2005). Such connectivity deficits observed here in bottom-up processes may thus underlie patients’ difficulties in judging the significance of emotional stimuli and responding accordingly.

Top-down processes

Impaired conflict monitoring, mediated by ACC dysfunction, has been proposed to play an important role in cognitive control deficits in schizophrenia patients (Kerns et al., 2005). Analogous to the ventral/dorsal distinction in the limbic system, the ACC has been divided into ‘cognitive’/dorsal and ‘affective’/ventral subdivisions (Bush et al, 2000; Mohanty et al., 2007). Consistent with previous literature, we found that incongruent compared with congruent trials were associated with reduced functional connectivity between dorsal and ventral ACC in healthy controls (Margulies et al., 2007) but with stronger functional coupling between ACC subregions in schizophrenia patients (Garrity et al., 2007; Hopmtan et al., 2010; Salvador et al., 2010). Such a lack of functional decoupling within the ACC during emotional conflict may relate to patients’ difficulty in apprehending ambiguous emotional information (Miller and Cohen, 2001; Egner and Hirsch, 2005; Speechley et al., 2013; Mitchell and Rossell, 2014; Patrick et al., 2016, 2015).

Similarly, the other top-down condition, i.e. the contrast of high vs low attentional demand, showed that schizophrenia patients, when compared with healthy controls, exhibited significantly reduced activation within the right DLPFC and higher task-related functional coupling between DLPFC and ventral ACC. An extensive literature has shown that prefrontal dysfunction constitutes a robust and critical pathophysiological feature in schizophrenia (Weinberger et al., 1992; Barch et al., 2003; Dichter et al., 2010; Taylor et al., 2012; Tully et al., 2014; Shin et al., 2015). The DLPFC is considered a key region in top-down modulation of stimulus processing (Miller and Cohen, 2001; Corbetta and Shulman, 2002), particularly by controlling the allocation of attentional resources (Price and Friston, 1999; MacDonald, 2000; Perlstein et al., 2001; Ramsey et al., 2002; Blasi et al., 2007). The decreased DLPFC BOLD signal we observed in patients may also be explained by treatment effects, as we noted an inverse correlation between DLPFC activity and antipsychotic dosage. It should be noted, however, that the literature is sparse and inconclusive regarding the influence of antipsychotics on prefrontal functioning (Honey et al., 1999; Snitz et al., 2005; Keedy et al., 2009), and our study design is not adequate for testing treatment effects.

In addition to reduced DLPFC BOLD signal, schizophrenia patients exhibited higher activity than controls in a set of regions including cuneus, precuneus, precentral gyrus and middle frontal gyrus during conditions of high attentional load. Interestingly, earlier neuroimaging studies (Fakra et al., 2008; Mukherjee et al., 2014), as well as a recent meta-analysis (Taylor et al., 2012), have found these regions to be more strongly activated in schizophrenia patients during emotional processing, even though they are not usually solicited in emotional tasks. One may therefore speculate that the overrecruitment of these regions indicates compensatory processes meant to counterbalance ineffective DLPFC functioning when attentional demands increase. Alternatively, this distributed network of activation, or less ‘tuned’ activity, may indicate unstable cortical signal processing in the PFC, a characteristic feature of schizophrenia (Winterer et al., 2006). As such, attentional processes that specifically engage DLPFC in healthy subjects would instead recruit a broader set of ‘non-specialized’ brain regions in patients, coherent with the view of decreased functional segregation of prefrontal brain regions in schizophrenia.

This study has some limitations. The interpretation of our connectivity analyses must be considered within the context of the inherent limitations of functional connectivity measures. PPI connectivity analyses rely on statistical correlations and thus cannot indicate the directionality of regional influence. Nonetheless, we believe that theory and previous research lay a reasonable foundation for the model presented. Indeed, numerous studies support the view that the amygdala facilitates perceptual processing of emotion-laden stimuli especially negative ones by biasing attention through bottom-up influences on higher attentional control regions (LeDoux, 2000; Davis and Whalen, 2001; Phelps, 2006). Concurrently, a growing literature indicates that cognitive processes such as distraction, reappraisal or even emotional conflict resolution can regulate emotional responses through top-down negative effects on amygdala activity (Ochsner and Gross, 2005; Etkin et al., 2006; McRae et al., 2010; Kanske et al., 2011; Ochsner et al., 2012). Additionally, we were able to relate PPI results to behavior performances within the various conditions under study, thus strengthening our findings. Interestingly, correlations between connectivity indices and performances in the behavioral task confirmed our expectations: when switching to the increased difficulty-load condition (i.e. positive to negative stimuli or low-attention to high-attention stimuli), executing the task required greater connectivity and was associated with longer RTs as well as lower accuracy. This stood true for both healthy controls and patients. However, in the congruency contrast, decoupling of the ACC subregions was associated with better accuracy in healthy controls but not in patients (Supplementary Information).

In summary, the current findings demonstrate that schizophrenia is associated with disturbed functional connectivity within the cortico-limbic system during emotional processing. These abnormal patterns of connectivity comprise a loss of coupling in amygdala-PFC circuits during bottom-up emotional processes associated with increased connectivity between the ventral affective and the dorsal cognitive subcircuits during top-down emotional control. Functional disconnection has been widely implicated as a core pathological factor in schizophrenia. Studies of functional connectivity disturbance in schizophrenia have found changes in a wide variety of brain systems, many of which involve prefrontal brain regions (Cole et al., 2011; Pettersson-Yeo et al., 2011; Fornito et al., 2012). Although decreases in functional connectivity are more commonly reported (Lynall et al., 2010; Zalesky et al., 2010), there is a substantial number of studies describing functional connectivity increases within frontal regions in schizophrenia patients and non-
affected first degree relatives, both at rest and during the execution of cognitive tasks (Whitfield-Gabrieli et al., 2009; Skudlarski et al., 2010; Sambataro et al., 2012). Fornito and Bullmore (2015) recently proposed an explanatory framework for brain dysconnection in schizophrenia, suggesting that neurodevelopmentally driven reductions in anatomical connectivity, especially within associative areas that constitute hubs integrating information from different network components, could dysregulate communication across widespread areas. This would lead to complex alterations in brain dynamics including both abnormal hypo- and hyperconnectivity. In this model, connectivity increases may reflect a compensatory process for dysregulated signaling in specific parts of the network or may result from abnormal wiring of structural connections leading to a breakdown of normally segregated systems and a dedifferentiation of neural activity. Such mechanisms would appear in our results as both a diffuse pattern of activation (rather than a focused signal in the DLFFC) and aberrant amplified connectivity in the PFC, likely reflecting cortical hyperexcitability and resulting increased neural synchrony (Spencer et al., 2004).

Acknowledgement

The authors thank Irene Chriss for her correction of the English text.

Funding

This work was supported by research grants from Bristol-Myers Squibb Company and Otsuka Pharmaceutical Company, the Instituts thématiques multi-organismes (ITMO), Pierre Hourié foundation and the Fondation pour la Recherche Médicale (FDT20140931114 to M.C.).

Supplementary data

Supplementary data are available at SCAN online.

Conflict of interest

None declared.

References

American Psychiatric Association. (2000). Diagnostic and Statistical Manual of Mental Disorders, Revised 4th edn. Washington, DC: American Psychiatric Association.

Anticevic, A., Repovs, G., Barch, D.M. (2012). Emotion effects on attention, amygdala activation, and functional connectivity in schizophrenia. Schizophrenia Bulletin, 38(5), 967–80.

Anticevic, A., Repovs, G., Corlett, P.R., Barch, D.M. (2011). Negative and nonemotional interference with visual working memory in schizophrenia. Biological Psychiatry, 70(12), 1159–68.

Anticevic, A., Repovs, G., Krystal, J.H., Barch, D.M. (2012). A broken filter: prefrontal functional connectivity abnormalities in schizophrenia during working memory interference. Schizophrenia Research, 141(1), 8–14.

Anticevic, A., Tang, Y., Cho, Y.T., et al. (2014). Amygdala connectivity differs among chronic, early course, and individuals at risk for developing schizophrenia. Schizophrenia Bulletin, 40(5), 1105–16.

Anticevic, A., Van Snellenberg, J.X., Cohen, R.E., Repovs, G., Dowd, E.C., Barch, D.M. (2012). Amygdala recruitment in schizophrenia in response to aversive emotional material: a meta-analysis of neuroimaging studies. Schizophrenia Bulletin, 38(3), 608–21.

Armony, J.L., LeDoux, J.E. (1997). How the brain processes emotional information. Annals of the New York Academy of Sciences, 821, 259–70.

Barch, D.M., Sheline, Y.I., Csernansky, J.G., Snyder, A.Z. (2003). Working memory and prefrontal cortex dysfunction: specificity to schizophrenia compared with major depression. Biological Psychiatry, 53(5), 376–84.

Blasi, G., Goldberg, T.E., Elvevåg, B., et al. (2007). Differentiating allocation of resources and conflict detection within attentional control processing. The European Journal of Neuroscience, 25(2), 594–602.

Blasi, G., Popolizio, T., Taurisano, P., et al. (2009). Changes in prefrontal and amygdala activity during olanzapine treatment in schizophrenia. Psychiatry Research – Neuroimaging, 173(1), 31–8.

Brett, M., Anton, J., Valabregue, R., Poline, J. (2002). Region of interest analysis using an SPM toolbox [Abstract]. In: 8th International Conference on Functional Mapping of the Human Brain. Available on CD-ROM in Neuroimage, 16. Craik, F.I.M., Lockhart, R.S. (1972). Levels of processing: a framework for memory research. Journal of Verbal Learning and Verbal Behavior, 11, 671–84.

Buckholz, J.W., Meyer-Lindenberg, A. (2012). Psychopathology and the human connectome: toward a transdiagnostic model of risk for mental illness. Neuron, 74(6), 990–1004.

Bush, G., Luu, P., Posner, M. (2000). Cognitive and emotional influences in anterior cingulate cortex. Trends in Cognitive Sciences, 4(6), 215–22.

Callicott, J.H., Bertolino, A., Mattay, V.S., et al. (2000). Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. Cerebral Cortex, 10(11), 1078–92.

Cole, M.W., Anticevic, A., Repovs, G., Barch, D. (2011). Variable global dysconnectivity and individual differences in schizophrenia. Biological Psychiatry, 70(1), 43–50.

Comte, M., Schon, D., Coull, J.T., et al. (2014). Dissociating bottom-up and top-down mechanisms in the cortico-limbic system during emotion processing. Cerebral Cortex, 26(1), 144–55.

Corbetta, M., Shulman, G.L. (2002). Control of goal-directed and stimulus-driven attention in the brain. Nature Reviews Neuroscience, 3(3), 201–15.

Das, P., Kemp, A.H., Flynn, G., et al. (2007). Functional disconnections in the direct and indirect amygdala pathways for fear processing in schizophrenia. Schizophrenia Research, 90(1–3), 284–94.

Davidson, R.J.R., Irwin, W. (1999). The functional neuroanatomy of emotion and affective style. Trends in Cognitive Sciences, 3(1), 11–21.

Davis, M., Whalen, P.J. (2001). The amygdala: vigilance and emotion. Molecular Psychiatry, 6(1), 13–34.

Delgado, M.R., Nearing, K.I., Ledoux, J.E., Phelps, E.A. (2008). Neural circuitry underlying the regulation of conditioned fear and its relation to extinction. Neuron, 59(5), 829–38.

Dichter, G.S., Bellion, C., Casp, M., Belger, A. (2010). Impaired modulation of attention and emotion in schizophrenia. Schizophrenia Bulletin, 36(3), 595–606.

Egner, T., Hirsch, J. (2005). Cognitive control mechanisms resolve conflict through cortical amplification of task-relevant information. Nature Neuroscience, 8(12), 1784–90.

Etkin, A., Egner, T., Peraza, D.M., Kandel, E.R., Hirsch, J. (2006). Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. Neuron, 51(6), 871–82.

Fakra, E., Salgado-Pineda, P., Delaveau, P., Hariri, A.R., Blin, O. (2008). Neural bases of different cognitive strategies for facial
affect processing in schizophrenia. Schizophrenia Research, 100(1–3), 191–205.

First, M., Spitzer, R., Gibbon, M., Williams, J. (2002). Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-Patient Edition. (SCID-I/NP). New York: Biometrics Research, New York State Psychiatric Institute.

Poland, L.C., Altschuler, L.L., Bookheimer, S.Y., Eisenberger, N., Townsend, J., Thompson, P.M. (2008). Evidence for deficient modulation of amygdala response by prefrontal cortex in bipolar mania. Psychiatry Research, 162(1), 27–37.

Fornito, A., Bullmore, E.T. (2015). Reconciling abnormalities of brain network structure and function in schizophrenia. Current Opinion in Neurobiology, 30, 44–50.

Fornito, A., Zalesky, A., Pantelis, C., Bullmore, E.T. (2012). Schizophrenia, neuroimaging and connectomics. Neuronlmage, 62(4), 2296–314.

Friston, K.J., Frith, C.D. (1995). Schizophrenia: a disconnection syndrome?. Clinical Neuroscience, 3(2), 89–97.

Garrity, A.G., Pearlson, G.D., McKiernan, K., Lloyd, D., Kiehl, K.A., Calhoun, V.D. (2007). Aberrant "default mode" functional connectivity in schizophrenia. American Journal of Psychiatry, 164(3), 450–7.

Goldin, P.R., McRae, K., Ramel, W., Gross, J.J. (2008). The neural bases of emotion regulation: reappraisal and suppression of negative emotion. Biological Psychiatry, 63(6), 577–86.

Gur, R.E., McGrath, C., Chan, R.M., Goldin, P.R., McRae, K., Ramel, W., Gross, J.J. (2008). The neural modulation of the amygdala response to fearful stimuli. Schizophrenia Research, 53, 44–50.

Kanske, P., Heissler, J., Schönfelder, S., Bongers, A., Wessa, M., Frangou, S. (2012). Abnormal functional activation and connectivity in the working memory network in early-onset schizophrenia. Journal of the American Academy of Child and Adolescent Psychiatry, 51(9), 911–20.

Lan, R.D., Reiman, E.M., Bradley, M.M., et al. (1997). Neuroanatomical correlates of pleasant and unpleasant emotion. Neuropsychologia, 35(11), 1437–44.

Lang, P.J., Bradley, M.M., Cuthbert, B.N. (2008). International Affective Picture System (IAPS): Affective Ratings of Pictures and Instruction Manual. Technical Report A-8. University of Florida, Gainesville, FL.

LeDoux, J.E. (2000). Emotion circuits in the brain. Annual Review of Neuroscience, 23, 155–84.

Lieberman, M.D., Cunningham, W.A. (2009). Type I and type II error concerns in fMRI research: re-balancing the scale. Social Cognitive and Affective Neuroscience, 4(4), 423–8.

Lindenmayer, J.P., Grochowski, S., Hyman, R.B. (1995). Five factor model of schizophrenia: replication across samples. Schizophrenia Research, 14(3), 229–34.

Liu, H., Tang, Y., Womer, F., et al. (2014). Differentiating patterns of amygdala-fugal functional connectivity in schizophrenia and bipolar disorder. Schizophrenia Bulletin, 40(2), 469–77.

Lynall, M.E., Bassett, D.S., Kerwin, R., et al. (2010). Functional connectivity and brain networks in schizophrenia. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 30(28), 9477–87.

MacDonald, A.W. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science, 288(5472), 1835–8.

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. Neuronlmage, 19(3), 1233–9.

Margulies, D.S., Kelly, A.M.C., Uddin, L.Q., Biswal, B.B., Castellanos, F.X., Milham, M.P. (2007). Mapping the functional connectivity of anterior cingulate cortex. Neuronlmage, 37(2), 579–88.

McLaren, D.G., Ries, M.L., Xu, G., Johnson, S.C. (2012). A generalized form of context-dependent psychophysiological interactions (gPPI): a comparison to standard approaches. Neuronlmage, 61(4), 1277–86.

McRae, K., Hughes, B., Chopra, S., Gabrieli, J.D.E., Gross, J.J., Ochsner, K.N. (2010). The neural bases of distraction and reappraisal. Journal of Cognitive Neuroscience, 22(2), 248–62.

Miller, E.K., Cohen, J.D. (2001). An integrative theory of prefrontal cortex function. Annual Review of Neuroscience, 24, 167–202.

Mitchell, R.L.C., Rossell, S.L. (2014). Perception of emotion-related conflict in human communications: what are the effects of schizophrenia?. Psychiatry Research, 220(1–2), 135–44.

Modinos, G., Ormel, J., Alemán, A. (2010). Altered activation and functional connectivity of neural systems supporting cognitive control of emotion in psychosis proneness. Schizophrenia Research, 118(1–3), 88–97.

Mohanty, A., Engels, A.S., Herrington, J.D., et al. (2007). Differential engagement of anterior cingulate cortex in subjects with schizophrenia. The American Journal of Psychiatry, 162(10), 1833–9.
subdivisions for cognitive and emotional function. Psychophysiology, 44(3), 343–51.
Monk, C.S., Telzer, E.H., Mogg, K., et al. (2008). Amygdala and ventrolateral prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. Archives of General Psychiatry, 65(5), 568–76.
Morris, R.W., Sparks, A., Mitchell, P.B., Weickert, C.S., Green, M.J. (2012). Lack of cortico-limbic coupling in bipolar disorder and schizophrenia during emotion regulation. Translational Psychiatry, 2(3), e90.
Mukherjee, P., Whalley, H.C., McKirdy, J.W., et al. (2014). Altered amygdala connectivity within the social brain in schizophrenia. Schizophrenia Bulletin, 40(1), 152–60.
O’Reilly, J.X., Woolrich, M.W., Behrens, T.E.J., Smith, S.M., Johansen-Berg, H. (2012). Tools of the trade: psychophysiological interactions and functional connectivity. Social Cognitive and Affective Neuroscience, 7(5), 604–9.
Ochsner, K.N., Gross, J.J. (2005). The cognitive control of emotion. Trends in Cognitive Sciences, 9(5), 242–9.
Ochsner, K.N., Silvers, J.A., Buhle, J.T. (2012). Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. Annals of the New York Academy of Sciences, 1251, E1–24.
Oldfield, R.C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia, 9, 97–113.
Paradiso, S., Andreasen, N.C., Crespo-Facorro, B., et al. (2003). Emotions in unmedicated patients with schizophrenia during evaluation with positron emission tomography. American Journal of Psychiatry, 160(10), 1775–83.
Park, I.H., Park, H.J., Chun, J.W., Kim, E.Y., Kim, J.J. (2008). Dysfunctional modulation of emotional interference in the medial prefrontal cortex in patients with schizophrenia. Neurosciences Letters, 440(2), 119–24.
Patrick, R.E., Christensen, B.K., Smolewska, K. (2016). Inhibiting reactions to emotional versus non-emotional response cues in schizophrenia: insights from a motor-process paradigm. Journal of Neuropsychology, 10(1), 59–76.
Patrick, R.E., Rastogi, A., Christensen, B.K. (2015). Effortful versus automatic emotional processing in schizophrenia: insights from a face-vignette task. Cognition and Emotion, 29(5), 1–17.
Perlstein, W.M., Carter, C.S., Noll, D.C., Cohen, J.D. (2001). Relation of prefrontal cortex dysfunction to working memory and symptoms in schizophrenia. American Journal of Psychiatry, 158(7), 1105–13.
Pettersson-Yeo, W., Allen, P., Benetti, S., McGuire, P., Mechelli, A. (2011). Dysconnectivity in schizophrenia: where are we now?. Neuroscience and Biobehavioral Reviews, 35(5), 1110–24.
Phan, K.L., Wager, T., Taylor, S.F., Liberzon, I. (2002). Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. NeuroImage, 16(2), 331–48.
Phelps, E.A. (2006). Emotion and cognition: insights from studies of the human amygdala. Annual Review of Psychology, 57, 27–53.
Phillips, M.L., Drevets, W.C., Rauch, S.L., Lane, R. (2003). Neurobiology of emotion perception I: the neural basis of normal emotion perception. Biological Psychiatry, 54(5), 504–14.
Phillips, M.L., Ladouceur, C.D., Drevets, W.C. (2008). A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. Molecular Psychiatry, 13(9), 829–57.
Price, C.J., Friston, K.J. (1999). Scanning patients with tasks they can perform. Human Brain Mapping, 8(2–3), 102–8.
Ramsey, N.F., Koning, H.A.M., Welles, P., Cahn, W., van der Linden, J.A., Kahn, R.S. (2002). Excessive recruitment of neural systems subserving logical reasoning in schizophrenia. Brain: A Journal of Neurology, 125(Pt 8), 1793–807.
Salgado-Pineda, P., Fakra, E., Delaveau, P., Hariri, A.R., Blin, O. (2010). Differential patterns of initial and sustained responses in amygdala and cortical regions to emotional stimuli in schizophrenia patients and healthy participants. Journal of Psychiatry and Neuroscience, 35(1), 41–8.
Salvador, R., Sarró, S., Gomar, J.J., et al. (2010). Overall brain connectivity maps show cortico-subcortical abnormalities in schizophrenia. Human Brain Mapping, 31(12), 2003–14.
Sambataro, F., Mattay, V.S., Thurin, K., et al. (2012). Altered cerebral response during cognitive control: a potential indicator of genetic liability for schizophrenia. Neuropsychopharmacology, 38(5), 846–53.
Satterthwaite, T.D., Wolf, D.H., Loughead, J., et al. (2010). Association of enhanced limbic response to threat with decreased cortical facial recognition memory response in schizophrenia. American Journal of Psychiatry, 167(4), 418–26.
Seifert, N.Y., Pauly, K., Kellermann, T., et al. (2009). Neuronal correlates of facial emotion discrimination in early onset schizophrenia. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology, 34(2), 477–87.
Shin, J.E., Choi, S.-H., Lee, H., Shin, Y.S., Jang, D.-P., Kim, J.-J. (2015). Involvement of the dorsolateral prefrontal cortex and superior temporal sulcus in impaired social perception in schizophrenia. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 58, 81–8.
Skudlarski, P., Jagannathan, K., Anderson, K., et al. (2010). Brain connectivity is not only lower but different in schizophrenia: a combined anatomical and functional approach. Biological Psychiatry, 68(1), 61–9.
Snitz, B.E., MacDonald, A., Cohen, J.D., et al. (2005). Lateral and medial hypofrontality in first-episode schizophrenia: functional activity in a medication-naïve state and effects of short-term atypical antipsychotic treatment. American Journal of Psychiatry, 162(12), 2322–9.
Speckley, W.J., Woodward, T.S., Ngan, E.T. (2013). Failure of conflict to modulate central executive network activity associated with delusions in schizophrenia. Frontiers in Psychiatry, 4, 113.
Spencer, K.M., Nestor, P.G., Perlmutter, R., et al. (2004). Neural synchrony indexes disordered perception and cognition in schizophrenia. Proceedings of the National Academy of Sciences of the United States of America, 101(49), 17288–93.
Stephan, K.E., Baldegw, T., Friston, K.J. (2006). Synaptic plasticity and dysconnection in schizophrenia. Biological Psychiatry, 59(10), 929–39.
Takahashi, H., Koeda, M., Oda, K., et al. (2004). An fMRI study of differential neural response to affective pictures in schizophrenia. NeuroImage, 22(3), 1247–54.
Taylor, S.F., Kang, J., Brege, I.S., Tso, I.F., Hosanagar, A., Johnson, T.D. (2012). Meta-analysis of functional neuroimaging studies of emotion perception and experience in schizophrenia. Biological Psychiatry, 71(2), 136–45.
Taylor, S.F., Phan, K.L., Britton, J.C., Liberzon, I. (2005). Neural response to emotional salience in schizophrenia. Neuropsychopharmacology, 30(5), 984–95.
Tottenham, N., Tanaka, J.W., Leon, A.C., et al. (2009). The NimStim set of facial expressions: judgments from untrained research participants. Psychiatry Research, 168(3), 242–9.
Townsend, J.D., Torrisi, S.J., Lieberman, M.D., Sugar, C.A., Bookheimer, S.Y., Altschuler, L.L. (2013). Frontal-amygdala
connectivity alterations during emotion downregulation in bipolar I disorder. Biological Psychiatry, 73(2), 127–35.

Tully, L.M., Lincoln, S.H., Hooker, C.I. (2014). Lateral prefrontal cortex activity during cognitive control of emotion predicts response to social stress in schizophrenia. NeuroImage: Clinical, 6, 43–53.

van der Meer, L., Swart, M., Van Der Velde, J., et al. (2014). Neural correlates of emotion regulation in patients with schizophrenia and non-affected siblings. PloS One, 9(6), e99667.

Weinberger, D.R., Berman, K.F., Suddath, R., Fuller Torrey, E. (1992). Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: a magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins. American Journal of Psychiatry, 149(7), 890–7.

Weinberger, D.R., Berman, K.F., Zec, R.F. (1986). Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. I. Regional Cerebral Blood Flow Evidence. Archives of General Psychiatry, 43(2), 114–24.

Whalen, P.J., Rauch, S.L., Etcoff, N.L., McInerney, S.C., Lee, M.B., Jenike, M.A. (1998). Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 18(1), 411–8.

Whitfield-Gabrieli, S., Thermens, H.W., Milanovic, S., et al. (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 of the United States of America, 106(4), 1279–84.

Winterer, G., Musso, F., Beckmann, C., et al. (2006). Instability of prefrontal signal processing in schizophrenia. The American Journal of Psychiatry, 163(11), 1960–8.

Woods, S.W. (2003). Chlorpromazine equivalent doses for the newer atypical antipsychotics. Journal of Clinical Psychiatry, 64(6), 663–7.

Yung, A.R., McGorry, P.D. (1996). The prodromal phase of first-episode psychosis: past and current conceptualizations. Schizophrenia Bulletin, 22(2), 353–70.

Zalesky, A., Fornito, A., Bullmore, E.T. (2010). Network-based statistic: identifying differences in brain networks. NeuroImage, 53(4), 1197–207.