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

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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.

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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 dysconnection 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; Fakra *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 (Kyriakopoulos *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

Table 1. Sociodemographic and clinical characteristics of participants

	Schizophrenia patients ($N = 26$)	Healthy controls ($N = 26$)	P
Age (years)	32.31 (8.87)	32.65 (7.68)	0.88
Gender(male/female)	17/9	17/9	1
Educational level (years)	12.0 (2.57)	12.85 (1.59)	0.16
NART score (premorbid IQ)	25.5 (7.4)	28.5 (5.2)	0.10
Aripiprazole (*N*)	15		
Risperidone (*N*)	11		
Chlorpromazine equivalents (mg/day)	274.36 (139.07)		
Total PANSS score	46.65 (18.09)		
Positive factor	8.04 (5.02)		
Negative factor	13.04 (7.32)		
Excitation factor	2.81 (3.45)		
Cognitive factor	9.27 (3.93)		
Depression factor	5.19 (3.0)		

Notes: Means are presented with s.d.'s in parentheses. PANSS, Positive and Negative Syndrome Scale; IQ, intelligence quotient; NART, National Adult Reading Test.

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.*, 2009). The peripheral part, on which face images were superimposed, represented scenes with pleasant or unpleasant emotional content, extracted from international affective picture system (IAPS) files (Lang *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) or 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-echoplanar imaging sequence (TR = 3000 ms; echo time (TE) = 30 ms; field-of- view (FOV) = 192 × 192 mm; 64 × 64 matrix; flip angle 84.8°; voxel size $3 \times 3 \times 3\,mm^3$). 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 ms; TE = 4.42 ms; inversion time (TI) = 800 ms; 256 × 256 × 180 matrix; flip angle 30°, voxel size $1 \times 1 \times 1\,mm^3$).

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 level [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 variations 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 eigenvariate 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, excitation 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, $P \leq 0.001$). 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, $P \leq 0.001$). 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; $k = 35$; $T = 3.73$; $P \leq 0.005$) and ventral ACC (x, y, z = 8, 34, −10; $k = 16$; $T = 3.54$; $P \leq 0.005$), as well as left DLPFC (x, y, z = −46, 8, 22; $k = 30$; $T = 3.45$; $P \leq 0.005$). 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; $k = 37$; $T = 4.22$; $P \leq 0.005$; x, y, z 6, 46, 16; $k = 23$; $T = 3.33$; $P \leq 0.005$; and x, y, z 4 22 −8; $k = 12$; $T = 3.29$; $P \leq 0.005$). 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; $k = 29$; $T = 3.14$; $P \leq 0.005$) (Figure 1).

Furthermore, there was a significant negative correlation between DLPFC activity in high attentional condition compared

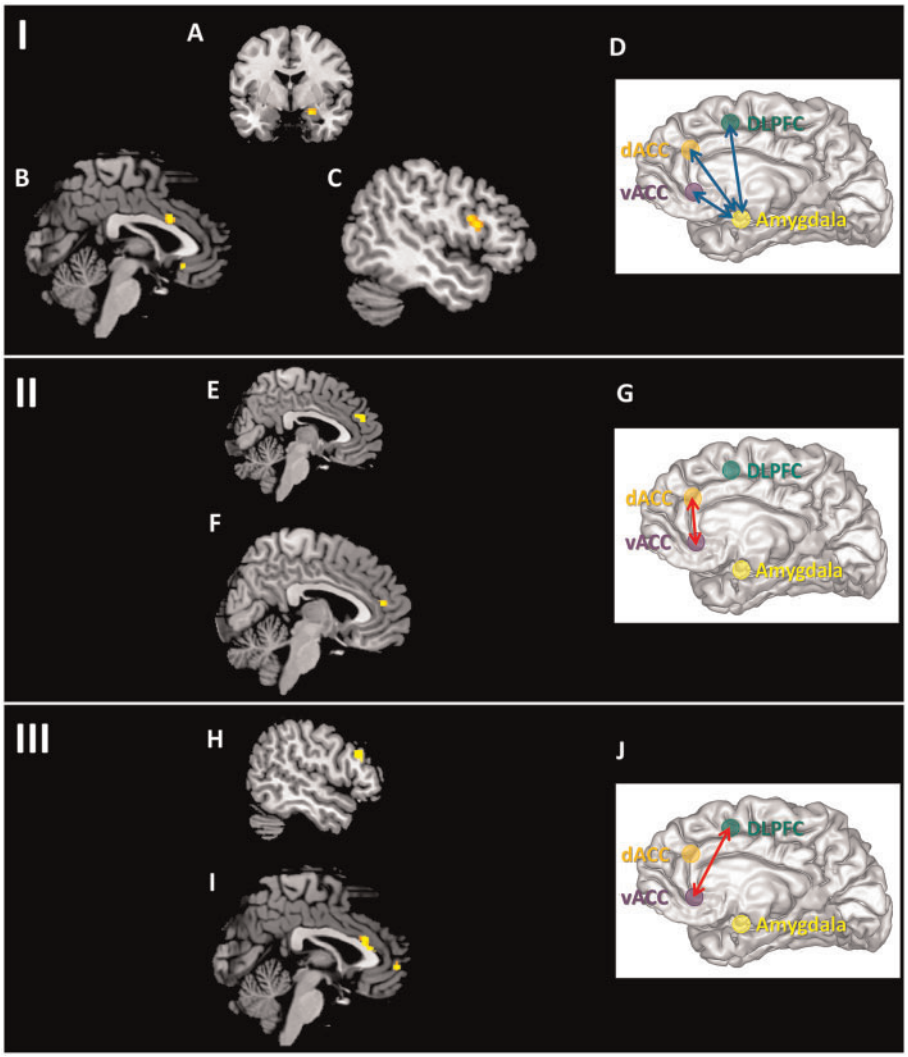

Fig. 1. Functional connectivity analyses. Upper panel (I): voxels in ACC (B) and in left DLPFC (C) that show lower connectivity with the right amygdala (A) in schizophrenia patients compared with healthy controls. (D) Schematic representation of between-group differences in amygdala functional connectivity as a function of valence; the blue arrows represent decreased connectivity in patients compared with controls. Middle panel (II): voxels in the ventral ACC (F) that show stronger connectivity with the dorsal ACC (E) 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 (I) that show stronger connectivity with the right DLPFC (H) 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).

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

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; Hoptman *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 process 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 dysconnection 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 DLPFC) and aberrant amplified connectivity in the PFC, likely reflecting cortical hyperexcitability and resulting increased neural synchrony (Spencer *et al*., 2004).

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Supplementary data

Supplementary data are available at *SCAN* online.

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