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Abnormal cortico-limbic connectivity during emotional processing correlates with symptom severity in schizophrenia

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ABSTRACT

Background: Impaired emotional processing is a core feature of schizophrenia (SZ). Consistent findings suggested that abnormal emotional processing in SZ could be paralleled by a disrupted functional and structural integrity within the fronto-limbic circuitry. The effective connectivity of emotional circuitry in SZ has never been explored in terms of causal relationship between brain regions. We used functional magnetic resonance imaging and Dynamic Causal Modeling (DCM) to characterize effective connectivity during implicit processing of affective stimuli in SZ.

Methods: We performed DCM to model connectivity between amygdala (Amy), dorsolateral prefrontal cortex (DLPFC), ventral prefrontal cortex (VPFC), fusiform gyrus (FG) and visual cortex (VC) in 25 patients with SZ and 29 HC. Bayesian Model Selection and average were performed to determine the optimal structural model and its parameters.

Results: Analyses revealed that patients with SZ are characterized by a significant reduced top-down endogenous connectivity from DLPFC to Amy, an increased connectivity from Amy to VPFC and a decreased driving input to Amy of affective stimuli compared to HC. Furthermore, DLPFC to Amy connection in patients significantly influenced the severity of psychopathology as rated on Positive and Negative Syndrome Scale.

Conclusions: Results suggest a functional disconnection in brain network that contributes to the symptomatic outcome of the disorder. Our findings support the study of effective connectivity within cortico-limbic structures as a marker of severity and treatment efficacy in SZ.

1. Introduction

Impaired emotional processing is a core feature of schizophrenia (SZ). Despite an apparently reduced expression of emotions, patients describe a vivid subjective emotional experience [33] with higher sensitivity for negative affects [27]. This altered emotional processing contributes to impairments in social cognition and psychosocial functioning [26,72].

Structural and functional brain imaging studies helped to define the core neural circuitries engaged in emotion processing. The activation of this circuitry relies upon a correct perception of the stimuli. In case of emotional faces, these are initially elaborated by visual cortex (VC) and fusiform gyrus (FG), areas deeply involved in processing emotionally connoted faces [19]. These areas project to other regions, parts of a wide circuitry, that includes limbic structures, such as amygdala, and frontal cortical areas, as dorsolateral (DLPFC), medial and ventral prefrontal regions (VPFC) [11,13,62]. The amygdala (Amy) is deeply involved in face processing and necessary for perceiving affective novelty and salience of the stimuli [1,34,74], and for identifying signals of threat and fear [35]. DPFC exerts a high-order and cognitive regulation of affects and emotions, and orients goal states and

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related behaviors [8,11]. VPFC is engaged in a rapid detailed evaluation of emotional stimuli and their contextual significance [29,44,54]. Both these frontal regions are recruited in active self-regulation and interact in modulating the amygdala reactivity [4,45,50,59,70]. Functional and structural alterations within the emotional circuitry have been constantly reposted in patients with SZ [5,9,22,25,37,55,67,76].

At the network level, it has been suggested that an abnormal connectivity among brain regions, with a failure to engage cortico-limbic structures in the automatic processing of emotions, could be a core underpinning of the emotional deficits associated with schizophrenia. In the last two decades several authors focused their attention on a 'disconnection' hypothesis for SZ. Specifically, it suggests that the core symptoms of this disorder can result from an abnormal functional and structural integration between distinct brain regions, such as cortical, limbic and temporal areas [16,48,64,75]. This hypothesis has been explored investigating the functional and effective connectivity (EC) between selected brain regions in SZ. Results have been very promising: the connectivity between PFC and Amy was reduced during the resting state [39], and absent [14,36], reversed [7] or decreased [58] during the processing of emotional stimuli. A reduced PFC-Amy coupling was also associated with psychosis proneness in the general population [43]. Remarkably, in schizophrenic patients the reduced functional connectivity between cortico-limbic structures, including PFC, temporal lobe, parahippocampal cortex and Amy, was positively related to behavioral measures of emotional regulation [15].

However, some methodological limitations hampered the interpretation of these pivotal findings. The methods used to measure connectivity, such as Psycho-Physiological Interactions and correlations between neural responses in seed areas, do not allow to infer casual relationships between activations in the studied regions [17]. An alternative method, Dynamic Casual Modeling (DCM), offers a deeper comprehension of the connectivity, thanks to the possibility of modeling the direction of causality between regions. Diwadkar explored with DCM the effective connectivity in adolescents at risk for SZ during affective processing [11]. The risk group showed a decreased input of the stimuli in visual cortex, a reduced connectivity and an increased inhibition in fronto-limbic connections. These data suggest that the abnormal connectivity within the emotional circuitry in SZ may identify an intermediate phenotype between the genetic liability of the disorder and its psychopathological outcome.

Although a disrupted connectivity within emotional circuitry may contribute to the neurobiological and psychopathological features of the disorder, no previous study explored the effective connectivity within this network in terms of causal relationships between seed regions. Thus, this study is aimed at investigating with DCM the effective connectivity within a cortico-limbic network which engaged Amy, DLPFC, VPFC, fusiform gyrus (FG) and VC during emotional processing in patients with SZ and HC. We hypothesized that coupling parameters among these seed regions would be altered in SZ and related to its psychopathology.

2. Methods

2.1. Participants

The sample included 54 participants. We studied 25 consecutively admitted inpatients affected by chronic schizophrenia, undifferentiated subtype [DSM-IV criteria, Structured Clinical Interview for DSM-IV (SCID-I) interview]. Exclusion criteria were additional diagnoses on Axis I, mental retardation on Axis II, pregnancy, major medical and neurological disorders, history of drug or alcohol abuse or dependency. Twenty-nine healthy participants, comparable for age and sex, served as controls.

Severity of current symptoms was rated on the Positive and Negative Syndrome Scale, PANSS [32].

After a complete description of the study to the participants, written informed consent was obtained. The study was approved by the local ethical committee.

2.2. Image acquisition and cognitive activation paradigm

Gradient echo and echo-planar images (EPIs) were acquired on a 3.0 T scanner (Gyroscan Intera; Philips, The Netherlands) using a six-channel sensitivity encoding (SENSE) head coil. For each functional run, 124 T2*-weighted volumes were acquired using an EPI pulse sequence [repetition time (TR) = 3000 ms, echo time (TE) = 35 ms, flip angle = 90°, field of view = 230 mm, number of axial slices = 40, slice thickness = 5 mm, matrix size = 80 × 80 reconstructed up to 128 × 128 pixels]. Two dummy scans before fMRI acquisition allowed us to obtain longitudinal magnetization equilibrium. Total acquisition time was 6 min and 11 s. On the same occasion and using the same magnet 22 Turbo Spin Echo (Philips), T2 axial slices [repetition time (TR) = 3000 ms; echo time (TE) = 85 ms; flip angle = 90°; turbo factor 15; 5-mm thick, axial slices with a 512 × 512 matrix and a 230 × 230 mm field of view] were acquired to rule out brain lesions.

Neural correlates of implicit emotional processing were investigated with a face-matching paradigm [21]. This paradigm previously allowed researchers to define the effective connectivity within the emotional circuitry in healthy subjects and in clinical populations [21,49,61,62]. Four blocks of six pictures, each representing human faces with fearful or angry expressions, interspersed with five blocks of six pictures of geometric shapes, were shown to participants. Each picture is made up of two faces/shapes in the lower side and one in the upper part. Participants had to push a button on a response box to indicate which of the two images displayed in the lower side of the picture matched the one in the upper part. Task performances of the subjects were recorded. Images were displayed for 4 s interleaved by a black screen.

2.3. Image processing and second level fMRI analyses

All images were computed, overlaid on anatomic images, and analyzed using Statistical Parametric Mapping software (SPM8, Wellcome Department of Imaging Neuroscience, Institute of Neurology and the National Hospital for Neurology and Neurosurgery; London, England). Scans were corrected for slice timing and realigned for head movements. Images were then normalized to a standard EPI template volume based on the Montreal Neurological Institute (MNI) reference brain, and smoothed using a 10-mm full-width at half-maximum isotropic Gaussian kernel. The evoked hemodynamic responses were modeled as a delta function convolved with a hemodynamic response and its temporal derivative within the context of the General Linear Model (GLM). At the individual level we first compared (t-test, threshold $P < 0.001$) the face-matching condition with the shape-matching condition, thereby isolating regions engaged in the emotional processing of faces.

Group-level analyses were based on the single-subject contrast images. One-sample t-tests were used to investigate the main effect of the task and to identify the peaks of maximum activation for extracting time series in Amy, DLPFC, VPFC, FG, VC ($P < 0.001$). Given that Z maps generated by SPM for experiments with high statistical power are inaccurate when F or t is very large, the transformation of F variates into normal Z variates was performed with the MATLAB algorhythm provided in [28].

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2.4. Volume of interest

We selected a priori volumes of interest (Amy, DLPFC, VPFC, FG and VC) by considering their relevance in face and emotional processing [10,13,62]. To account for individual differences, we extracted the principal eigenvariates in 8 mm spheres centered, for each region of interest, on the local maxima of the subject-specific statistical maps. These centers had to be within 8 mm of the group-maxima univariate analysis, which were at MNI coordinates 56 34 18 for DLPFC (BA 46), at MNI 34 38 -18 for VPFC (BA 11), at MNI 26 -98 2 for VC (BA 18), and at MNI 40 -42 -24 for FG (BA 37). Amy was considered as a whole.

Our DCM analysis was restricted to the right hemisphere, because we had previously showed that schizophrenic patients mainly differed from HC for abnormal neural responses to emotional faces in the right hemisphere [5], and because of the general predominance of this hemisphere in processing of emotional faces [13]. The higher involvement of right hemisphere was also confirmed by the results of our second level analyses (see Results, Section 3.1). Seed regions were identified using Wake Forest PickAtlas software (www.fmri.wfubmc.edu).

2.5. Dynamic Causal Modeling

DCM is a hypothesis-driven analysis approach based a Bayesian model comparison procedure that allows to infer effective connectivity between seed brain areas in fMRI data [18]. DCM assesses the dynamic behaviour of specific brain regions regarding their causal relationships under the influence of external perturbations, such as the applied experimental conditions [61].

BOLD responses are modeled in DCM by a differential state equation, which describes (i) how the present state of one neuronal population causes dynamics (i.e., rate of change) in another via synaptic connections (intrinsic connections) and (ii) how these interactions change under the influence of external perturbations (i.e., how experimental manipulations as the emotional valence of faces modulate the strength of endogenous connections; modulatory effects) [66] and (iii) driving inputs, that could be considered as direct influences of the stimuli on the neural activity of involved regions (i.e. the visual stimuli on occipital cortex). After specifying and estimating different models, DCM analyses include a two-step procedure that involves (1) the selection of the best model for each group in terms of structure using Bayesian model Selection (BMS) and (2) the estimation of DCMs' parameters using Bayesian model averaging (BMA), which finally allows to test the hypothesis that DCMs' parameters significantly differ between groups.

The differential state equations were modeled on different seed regions of interest (Amy, DLPFC, VPFC, FG, VC in the right hemisphere).

2.6. Models specification

Forty-eight alternative models with different endogenous connections, task inputs and modulatory effects were constructed by using DCM12 (Fig. 1 for a schematic representation of the model space, and Supplementary materials for a more detailed one). All models were defined as bilinear. All visual stimuli (faces and geometric shapes) were modeled to drive activity in VC, and affective information may bypass this area via thalamus, directly activating FG and Amy [11]. Driving inputs in these areas (VC, Amy, FG) were set across all the models. In all the proposed models we fixed forward intrinsic connection from VC to FG, from FG to Amy, and from Amy to both DLPFC and VPFC. These a priori were based on primate and in vivo imaging studies and represent the bottom-up flow information in cortico-limbic circuitry [11,20,51]. Furthermore, converging neurobiological findings suggest a top-down

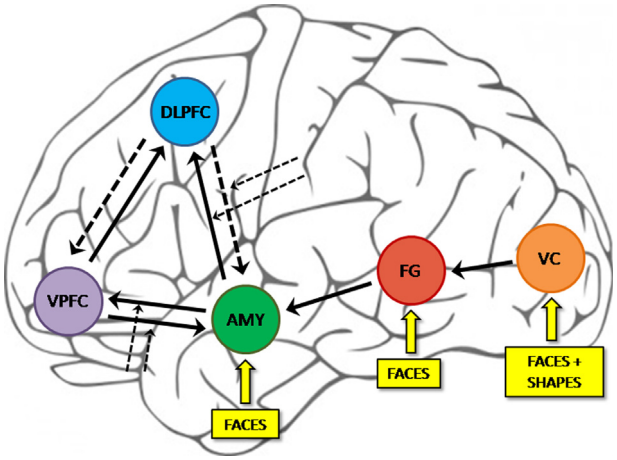

Fig. 1. Schematic graphic representation of model space for DCM analyses, composed by 48 competitive models for DCM. Yellow arrows represent driving inputs: visual stimuli (both affective faces and geometrical shapes) enter the network from VC, and only affective faces enter into FG and Amy. Fixed intrinsic connections (continues arrows) have been modeled in all DCMs: from VC to FG, from FG to Amy, from Amy to both DLPFC and VPFC, from VPFC to DLPFC and from VPFC to Amy. The 48 DCM models varied for: (1) the inclusion of intrinsic connection from DLPFC to VPFC and from both these areas to Amy, and for (2) the presence or absence of modulatory effects on the connections between PFC and Amy. The dashed arrows represent the parameters that varied across the models.

connection from VPFC to Amy [56,61,62] and from VPFC to DLPFC [62] cocomac database: http://cocomac.org. The 48 models varied for: (1) the inclusion of intrinsic connection from DLPFC to VPFC and from both these areas to Amy, and for (2) the presence or absence of modulatory effects on the connections between PFC and Amy. All the possible combinations between these parameters were modeled in a combinatorial approach ending in 48 DCMs.

2.7. Structural and parametric analyses

After constructing DCMs for each subject? we used Bayesian model selection (BMS) to compare the 48 models. BMS computes exceedance and posterior probabilities of the competitive models [65]. The exceedance probability of a given model denotes the probability that this model is more likely than any other model tested, given the data. Subsequently, we performed BMA to quantitatively summarize parameter estimates of intrinsic connections, modulatory effects and driving inputs. BMA averages each parameter across subjects and across models so that the contribution of each model (of each subject) for that parameter is weighted for the posterior probability of each model for each subject [47,66]. In both analyses were used the random effects (RFX) assuming parameters to be probabilistically distributed in the population [66]. BMA was performed separately for patients and HC.

After BMA, we extracted the individual estimates for connectivity parameters. They were included in a second level analysis to assess differences between groups. Group differences in the strength of each connection, modulatory effects and driving inputs were analyzed with a two-sample *t*-test. We applied Bonferroni-Holm correction to account for multiple comparisons [24].

To test the hypothesis that the connections which differed between patients and controls may have a relationship with the symptomatology of the disorder, we analyzed the effect of the strength of these significantly different connections on the PANSS rating for positive, negative and general symptoms. A multiple regression was performed in the context of the General Linear Model (GLM) [41,69] with strength of the connection as factors and PANSS subscales as within-subjects dependent variables [40], to test the statistical significance of the effect of the single

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Table 1
Clinical and demographic characteristics of the sample, and performance at the cognitive activation task.

	Controls (n = 38)	SZ patients (n = 24)	t, χ^2	P
Age	37.58 ± 12.14	33.64 ± 7.93	1.38	0.17
Gender	16 F, 13 M	10 F, 14 M	0.96	0.32
Age at onset	/	23.04 ± 5.61	/	/
Duration of illness	/	10.36 ± 7.79	/	/
PANSS-TOT	/	81.90 ± 18.98	/	/
PANSS-P	/	21 ± 4.77	/	/
PANSS-N	/	22.25 ± 4.91	/	/
PANNS-G	/	42.80 ± 7.73	/	/
Chlorpromazine equivalents	/	274.08 ± 145.89	/	/
Correct matches (faces) (n)	23.25 ± 2.30	20.29 ± 4.85	2.93	0.005*
Correct matches (figures) (n)	29.00 ± 1.71	20.29 ± 10.29	4.49	< 0.001*
Mean response latencies (s)	0.83 ± 1.23	0.58 ± 0.12	0.98	0.253

Data are mean ± standard deviations.
M: male; F: female; SZ: schizophrenic patients; PANSS: Positive and Negative Syndrome Scale; PANSS-TOT: PANSS Total Score; PANSS-N: PANSS negative symptoms sub-score; PANSS-P: PANSS positive symptoms sub-score; PANSS-G: PANSS general psychopathology sub-score. Age at onset and Duration of illness were calculated from the first psychotic episode. *P value < 0.05.

independent factors on the dependent variables by parametric estimates of predictor variables (least squares method). Analyses were performed using a commercially available software (StatSoft Statistica 6.0, Tulsa, OK, USA) and following standard computational procedures [23].

3. Results

3.1. Demographic and clinical characteristics and fMRI data

Demographic and clinical characteristics of the sample are summarized in Table 1. No significant differences between SZ and HC have been found. Patients had a significantly worse performance than HC, with non-significantly different response latencies.

Results of conventional second level fMRI analyses (one sample t-test) are summarized in Table 2. Among other brain regions, subjects significantly activated DLPFC (BA 46, peak MNI coordinates 56 34 18), VPFC (BA 11, peak MNI coordinates 34 38 -18), VC (BA 18, peak MNI coordinates 26 -98 2) and FG (BA 37, peak MNI coordinates 40 -42 -24), Amy (peak MNI coordinates 20 -12 -18).

3.2. Model structure: Bayesian Model selection

Random effect BMS showed the exceedance probability of each models (Fig. 2), identifying in model 45 (Fig. 3) the best fit within the evaluated model space of 48 models. The best model has bidirectional connections between the prefrontal areas and Amy, and forward connections from VPFC to DLPFC, from VC to FG, and from FG to Amy. The modulatory effects of the task have been found on the intrinsic connection between DLPFC and Amy, and on the connection from Amy to VPFC.

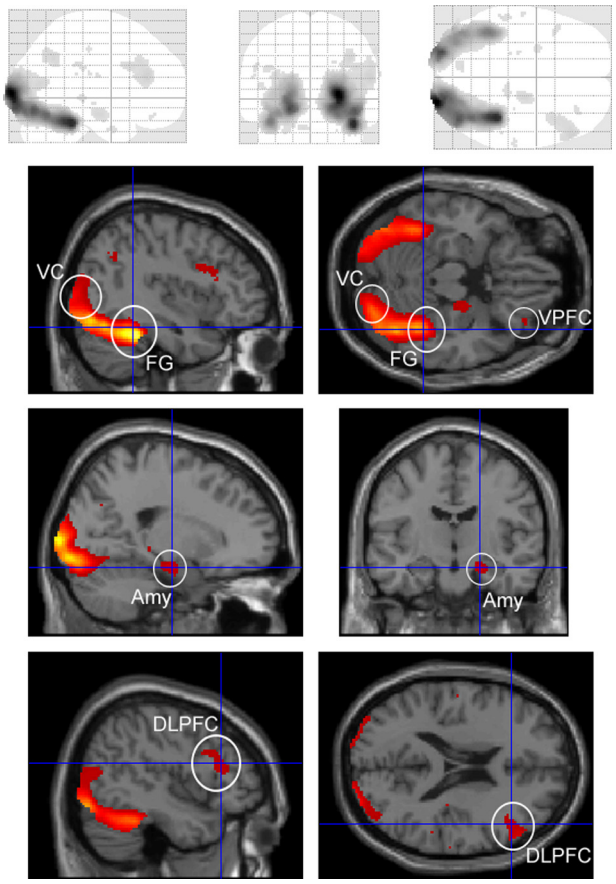

Fig. 2. Brain regions significantly activated by the task (one sample t-test). Data are shown for the main effects surviving a threshold of $P < 0.001$ in the whole brain. DLPFC: dorsolateral prefrontal cortex; FG: fusiform gyrus; Amy: amygdala; VC: visual cortex; VPFC: ventral prefrontal cortex.

3.3. Intrinsic connections

Patients with SZ showed significant reduced intrinsic connectivity from DLPFC to Amy (P = 0.001, corrected) and from VC to FG (P = 0.008, not surviving Bonferroni-Holm correction); and an increased connectivity from Amy to VPFC (P = 0.001, corrected) (Fig. 4, Table 3). DCM measures did not significantly correlate with task performance.

The GLM multiple regression showed a significant main effect of DLPFC to Amy on the three subscales of PANSS scores (F = 7.45, P = 0.014) due to a significant effect on the PANSS positive subscale

Table 2
Brain regions significantly activated by the task (one sample t-test).

Region	Cluster size	L/R	BA	Signal peak	F	Z
Middle occipital gyrus[a]	5521	Right	18	26 -98 2	199.85	8.94
Fusiform gyrus[a]	5521	Right	37	40 -42 -24	158.20	8.41
Lingual gyrus[a]	3546	Left		-22 -94-12	131.53	7.98
Middle frontal gyrus	507	Right	46	56 34 18	24.71	4.36
Angular gyrus	171	Right		36 -58 34	19.19	3.88
Amygdala	119	Right		20 -12 -18	18.68	3.83
Thalamus	23	Right		18 -30 -2	14.43	3.38
Middle temporal gyrus	11	Left	19	-50 -80 10	13.95	3.32
Middle frontal gyrus	9	Right	11	34 38 -18	13.85	3.31

Data are shown for the main effects surviving a threshold of $P < 0.001$ in the whole brain: Brodmann's area (BA): lateralization (L/R), MRIh coordinates (x, y, z) of voxels with higher Z values (signal peaks), and level of significance.
[a] Regions where significance survived a threshold of $P < 0.05$ FWE corrected for multiple comparisons.

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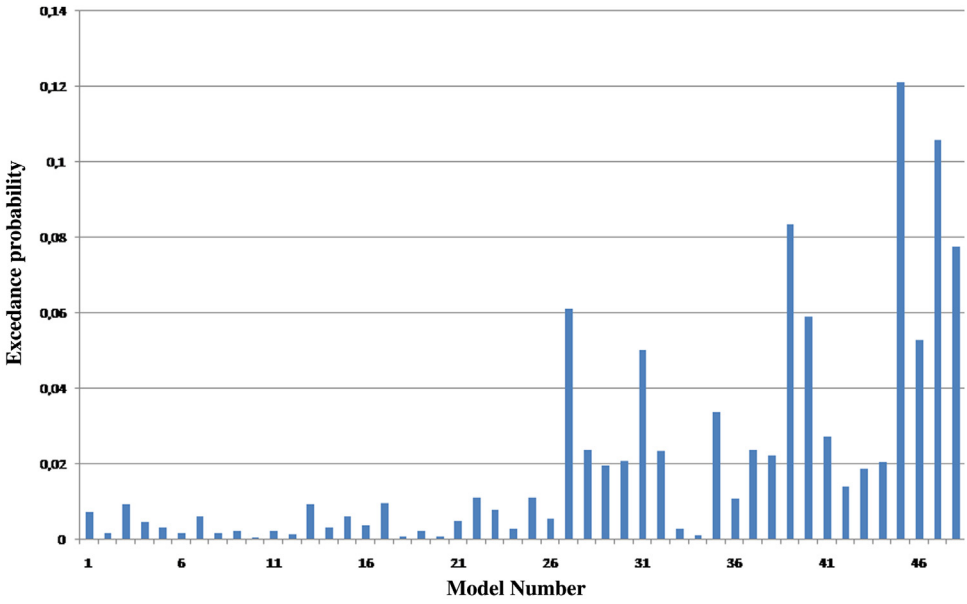

Fig. 3. Exceedance probability for the 48 DCM models.

(β = –0.47, t = 2.22, P = 0.040), a significant effect on the PANSS general subscale (β = –0.49, t = 2.36, P = 0.030), and marginal, non-significant effects on the PANSS negative subscale (β = –0.44, t = 2.02, P = 0.059). No main effects of Amy to VPFC connectivity were detected (F = 0.03, P = 0.87).

3.4. Driving input

The driving input of faces into Amy was significantly different between HC and patients with SZ (corrected P = 0.002) (Fig. 4 and Table 3). Although the absolute strength of the input was increased in HC, the two groups showed different pattern of driving input: in HC the input was inhibitory into Amy (in agreement with previous literature [61]), while in patients with SZ it showed a positive excitatory value. The strength of the input was not associated with PANSS scores.

Table 3
Results of the two sample t-tests comparing the DCM parameters between healthy controls and schizophrenic patients.

	SZ (n = 25)	Controls (n = 29)	t (1,52)	P
Intrinsic connections				
DLPFC to Amy	0.076 ± 0.099	0.173 ± 0.107	−3.406	0.0012*
Amy to DLPFC	0.109 ± 0.115	0.176 ± 0.095	−2.312	0.0247
VPFC to Amy	0.302 ± 0.155	0.186 ± 0.231	2.129	0.0379
Amy to VPFC	0.263 ± 0.115	0.133 ± 0.158	3.392	0.0013*
VPFC to DLPFC	0.158 ± 0.125	0.117 ± 0.077	−0.336	0.7379
DLPFC to VPFC	0.053 ± 0.054	0.064 ± 0.060	−0.670	0.5055
FG to Amy	0.080 ± 0.098	0.110 ± 0.087	−1.175	0.2453
VC to FG	0.255 ± 0.209	0.388 ± 0.141	−2.757	0.0080
Modulatory effects				
DLPFC to Amy	0.031 ± 0.045	0.022 ± 0.053	0.701	0.48
Amy to DLPFC	0.029 ± 0.056	0.023 ± 0.029	0.529	0.59
VPFC to Amy	0.030 ± 0.045	0.042 ± 0.070	−0.748	0.45
Amy to VPFC	0.028 ± 0.041	0.009 ± 0.031	1.924	0.05
Driving inputs				
VC (Face)	0.008 ± 0.006	0.008 ± 0.005	−0.106	0.9157
FG (Face)	−0.002 ± 0.006	−0.004 ± 0.005	1.497	0.1403
Amy (Face)	0.001 ± 0.030	−0.027 ± 0.035	3.193	0.002*
VC (Shape)	−0.001 ± 0.005	−0.002 ± 0.005	0.115	0.9088

Data are mean ± standard deviations. *= P values surviving Bonferroni-Holm correction for multiple comparisons.
SZ: schizophrenic patients; DLPFC: dorsolateral prefrontal cortex; FG: fusiform gyrus; Amy: amygdala; VC: visual cortex; VPFC: ventral prefrontal cortex.

3.5. Modulatory effects of affective faces on intrinsic connections

No significant difference between groups was observed in the modulatory effects of faces on the cortico-limbic connections (Table 3).

4. Discussion

This is the first study using DCM to explore the effective connectivity within the neural network involved in emotional regulation in patients with schizophrenia. We observed a reduced endogenous connectivity from DLPFC to Amy, and an increased bottom-up connectivity from Amy to VPFC. Endogenous connectivity refers to the intrinsic, task-independent effective connectivity between seed regions, while modulatory effects increase or decrease the endogenous connectivity during the execution of the emotional task [63]. In our sample, we observed task-dependent modulatory effects on the bidirectional connections between DLPFC and Amy, and from VPFC to Amy, in both HC and schizophrenic patients, who did not differ for these DCM parameters. A significantly decreased intrinsic connectivity with comparable modulatory effects suggests that the abnormal brain response to emotional stimuli in schizophrenia [5,9,22,25,37,55,67,76] may be associated with a general impairment of cortico-limbic connectivity not specifically related to the emotional processing tasks.

The decreased top-down effective connectivity from DLPFC to Amy in patients confirms the hypothesis of an abnormal functional integration between cortical and limbic areas in SZ [16,48,64,75] and could result in an altered inhibition of the Amy activity, which has been previously correlated with the intensity of the subjective experience of negative emotions [38,68]. DLPFC exerts a crucial role in the cognitive regulation of the emotional experience [52,53]. A reduced inhibition of Amy could then underpin the impaired cognitive control of emotions and enhanced sensitivity to negative stimuli observed in schizophrenic patients [5].

The impaired effective connectivity in SZ may contribute to the core symptomatology of the disorder. In agreement with the

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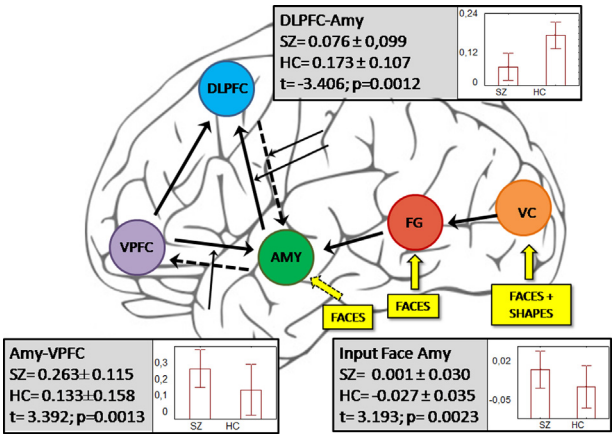

Fig. 4. Graphic representation of DCMs results. The best model has bidirectional connections between the prefrontal areas and Amy, and forward connection from VPFC to DLPFC, from VC to FG, and from FG to Amy. The modulatory effects of the task have been found on the intrinsic connection between DLPFC and Amy, and on the connection from Amy to VPFC. Patients with SZ showed significant reduced intrinsic connectivity from DLPFC to Amy, an increased connectivity from Amy to VPFC and a reduced driving input of affective faces into Amy (Bonferroni-Holm corrected; dotted arrows). Yellow arrows symbolize the driving inputs. Data are mean ± standard deviations. DLPFC: dorsolateral prefrontal cortex; FG: fusiform gyrus; Amy: amygdala; VC: visual cortex; VPFC: ventral prefrontal cortex.

'disconnection' hypothesis (see Introduction), we observed a significant negative effect of the strength of the top-down DLPFC-Amy connection on the severity of positive and general symptomatology as rated on PANSS: the lower the connectivity, the worse the observed severity of psychopathology. A reduced fMRI activity of DLPFC has been associated with loss of executive control in SZ [42], and our data suggest that its reduced inhibitory control of Amy reactivity may also be associated with difficulties in developing coherent and efficient strategies in terms of adaptive behavior [16], as expressed in the general PANSS symptoms of disorganization, disorientation, disturbance of volition, poor impulse control, lack of judgment and insight, unusual thought content. A reduced top-down control of subcortical structures involved in emotional regulation and attention, such as Amy, may enhance responsivity to emotional stimuli, hypervigilance, and mood lability, and has been proposed as a core neurocognitive underpinning of positive symptoms such as hostility, suspiciousness, grandiosity, delusions, and hallucinations [2].

Furthermore, the driving input of emotional stimuli into Amy, albeit reduced in schizophrenic patients compared to HC, exerts an excitatory role in SZ, opposite to the inhibitory pattern observed in HC. These results support a different effect of emotional faces in SZ compared to HC and might contribute to the reported hyperactivation of Amy in this disorder [5,25,46].

VPFC is involved in a detailed but more rapid evaluation of emotional stimuli and of their contextual significance [30,44,54]. VPFC also exerts an excitatory connection to DLPFC that may be engaged for a further and more efficient modulation of the limbic activity [3,53]. The increased bottom-up connection from Amy to VPFC might then underpin an automatic and rapid recruitment of prefrontal cortical structures in order to inhibit the Amy hyperactivity, also resulting from the reduced top-down DLPFC-Amy connectivity.

The overall abnormal connectivity within the cortico-limbic circuitry might not be limited to neural responses to emotional tasks, but could extend to other states of the brain, as suggested by the observation of altered connectivity in the resting state [39], in the default mode network [57], and during word encoding [77]. Current perspectives suggest that in schizophrenia such a general impairment in connectivity could be due or paralleled by structural alterations in grey and white matter structures [5]. Furthermore, our findings showed abnormalities of endogenous, intrinsic, task-independent effective connectivity in schizophrenic patients, which may associate with structural changes in the brain. Neuropathological abnormalities in grey matter include both quantitative (local volume changes; abnormal number, density and size of the neurons) and qualitative (cytoarchitectural upset, disarray of neuronal arrangement, and ectopic expression of neurons) alterations, leading to marked changes in local neuronal microcircuitry [31]. A growing literature also suggests a manifest disruption of the integrity of white matter tracts, possibly due to reduced axonal number or packing density, abnormal glial cell arrangement or function, and reduced myelin [12]. An abnormal microstructural integrity of white matter tracts in schizophrenic patients may reflect the presence of different abnormal processes among the neurobiological underpinnings of the disorder and a loss of synchronicity in signal transmission between brain regions. These may result in changes of effective connectivity and dysregulation of neural control systems [6]. Specifically, the reduced FA in frontal and temporal areas [60,73] likely has functional consequences for prefrontal-limbic communication [6]. Both structural and functional brain abnormalities may also represent aberrant developmental patterns associated with SZ, probably expression of a complex recursive interaction between genes and environment which evolves throughout the development into a progressive brain disconnection [71]. Future studies may be aimed at directly investigating the relationship between structural and effective connectivity in schizophrenia. Strengths of the present study include a focused research question, state-of-the-art imaging methods, and straightforward effects, but our results must be viewed in light of some methodological limitations. Patients were non drug-naive, and the drug treatments administered during the course of the illness could have influenced MRI measures. Recruitment was in a single center and in a single ethnic group, thus raising the possibility of population stratifications limiting the generalizability of findings. Nevertheless, these limitations do not bias the main finding that patients with SZ show an abnormal connectivity between areas engaged in the regulation of affective states and in the definition of the emotional significance of the stimuli [52,53], such as VPFC, DLPFC and Amy.

In conclusion, our findings suggest a functional disconnection in brain networks that contributes to the symptomatic outcomes of the disorder. The clinical relevance of these abnormalities, as suggested by the influence of connectivity on the severity of symptoms, supports the study of effective connectivity of cortico-limbic structures as a marker of severity and treatment efficacy in SZ.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eurpsy.2015.01.002.

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