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Neural correlates of delusion in bipolar depression

Daniele Radaelli [a,b,*], Sara Poletti [a,b], Irene Gorni [a], Clara Locatelli [a,b], Enrico Smeraldi [a,b], Cristina Colombo [a,b], Francesco Benedetti [a,b]

[a] Department of Clinical Neurosciences, Scientific Institute, University Vita-Salute San Raffaele, Milan, Italy
[b] Centro di Eccellenza Risonanza Magnetica ad Alto Campo (C.E.R.M.A.C.), University Vita-Salute San Raffaele, Milan, Italy

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ABSTRACT

Approximately one-half of all patients affected by bipolar disorder present psychotic features at least in one occasion. This factor worsens the personal and social burden of the disease. Several studies find an altered brain activity in mesolimbic and prefrontal regions in relation to aberrant attribution of salience to stimuli in delusional patients. The aim of the present study is to investigate gray matter (GM) structural correlates of the past history of delusions in a sample of bipolar patients. The sample includes 34 delusional and 39 non-delusional bipolar patients. Brain-imaging volumetric sequences were acquired on a 3.0 T scanner. Voxel based morphometry (VBM) was performed comparing delusional and non-delusional patients. VBM analysis found significant ($p=0.001$) differences in prefrontal areas and in the insula where delusional patients show lower GM volume compared to non-delusional patients. The main finding of the present study is a reduction of gray matter volume in the dorsolateral prefrontal cortex and in the insula of delusional patients. This result supports the hypothesis of abnormalities in salience and executive-control networks of delusional patients, which could be associated with an aberrant assignment of salience to the elements of one's own experience that is linked to delusion and psychotic symptoms.

1. Introduction

Approximately one-half of all patients affected by bipolar disorder present psychotic features, as defined by DSM-IV, in at least one occasion (Keck et al., 2003). This factor worsens the personal and social burden of the disease. Early treatment dramatically ameliorates poor prognosis and outcome of patients with psychotic features, reducing conversion rates to full-blown illness and decreasing symptoms severity (Salvadore et al., 2008). The identification of biological markers associated with the propensity to develop psychosis could help both to understand its psychobiological basis and to better shape individual treatment plans.

Different in vivo imaging studies found convincing evidences of dopamine dysregulation in acute psychosis (Guillin et al., 2007; Kumakura et al., 2007). It has been hypothesized that a dysregulation of the mesolimbic and prefrontal dopamine system may lead to aberrant attribution of salience and may contribute to the emergence of psychopathological symptoms like delusions (Kapur, 2003). Increased or chaotic firing of dopaminergic neurons in the striatum may lead to the attribution of salience to otherwise irrelevant stimuli (Heinz and Schlagenhauf, 2010). Recent findings also show that dopaminergic dysregulation in limbic areas contribute to the formation of delusions and negative symptoms (Pankow et al., 2012).

Salience is the state or quality by which something stands out from its neighbors. Saliency detection is considered to be a key attentional mechanism that facilitates learning and survival by enabling subjects to focus their limited perceptual and cognitive resources on the most pertinent subset of the available sensory data. Humans are constantly invested by stimuli from the inside and the outside world. In order to plan and direct actions and thoughts, our system has to integrate all these data from different sources. The neuropsychological construct of salience is considered a key mechanism in delusion formation and maintenance (Palaniyappan and Liddle, 2012).

Two dissociable networks that are critical for guidance of thought and behavior have been identified in humans. These networks include limbic/paralimbic emotional salience areas and dorsal neocortical executive control systems. For the attribution of salience, the proposed model includes a network built around limbic structures, most prominently the anterior cingulate cortex (ACC) and insula. These regions activate in response to various forms of salience, including emotional stimuli, empathy, metabolic stress, hunger,

* Correspondence to: Istituto Scientifico Ospedale San Raffaele, Department of Clinical Neurosciences, San Raffaele Turro, Via Stamira d'Ancona 20, Milano, Italy. Tel.: +39 02 2643 3156; fax: +39 02 26433 265.
E-mail address: radaelli.daniele@hsr.it (D. Radaelli).

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pleasurable and enjoyable cues, emotional faces and social rejection (Seeley et al., 2007). In contrast to emotional salience areas, the executive-control network operate on identified stimuli through directing attention to pertinent stimuli and behavioral choices (Seeley et al., 2007).

Functional magnetic resonance imaging (fMRI) studies frequently associated this network with delusion in both affective disorder and schizophrenia (Gradin et al., 2012; Palaniyappan et al., 2010). A significant reduction of gray matter (GM) volume in the dorsolateral and medial prefrontal cortex in bipolar patients with persecutory delusions was reported too (Tost et al., 2010). These areas have also been previously associated with the development of persecutory ideation in schizophrenia. Indeed previous functional imaging data suggest that deficits in medial prefrontal cortex (Blackwood et al., 2004; Sabri et al., 1997) and dorsolateral prefrontal cortex (DLPFC) are at the core of the development of persecutory delusions (Corlett et al., 2007).

If a state of aberrant salience is needed for the development of psychotic symptoms and if the attribution of salience requires activity in specific gray matter areas, it can be hypothesized that patients with and without psychotic symptoms could report differences in gray matter volume in these areas. Such an approach has proved successful in describing structural correlates of psychopathological symptoms in bipolar disorder for suicidality (Benedetti et al., 2011).

The present study aimed to evaluate through structural magnetic resonance imaging (sMRI) the structural gray matter correlates of delusion in a sample of patients affected by a major depressive episode, with or without psychotic feature, in course of Bipolar Disorder type I.

2. Method

2.1. Sample, treatment and clinical assessment

The sample included 73 participants. Thirty-four delusional and 39 non-delusional in-patients affected by Bipolar disorder and admitted to San Raffaele Hospital Psychiatric ward in Milan have been studied. No patients reported hallucinations. Patients with a positive history of delusion ($N=34$) where matched for sex and age with 39 patients who never showed delusion during current or previous episodes (Table 1). To be included in the study patients had to be diagnosed with bipolar disorder type I (Structured Clinical Interview for DSM Disorders, SCID I) with current depressive episode. Exclusion criteria were additional diagnoses on Axis I, mental retardation on Axis II, pregnancy, major medical and neurological disorders, or history of drug or alcohol abuse or dependency. No patient had received electroconvulsive therapy within 6 months before study enrollment. Physical examination, laboratory tests, and electrocardiograms were performed at admission. None of the patients showed psychotic features during the magnetic resonance acquisition. Patients were studied soon after hospitalization.

According to DSM-IV TR criteria, delusions were defined as "A false belief based on incorrect inference about external reality that is firmly sustained despite what almost everybody else believes and despite what constitutes incontrovertible and obvious proof or evidence to the contrary. The belief is not one ordinarily accepted by other members of the person's culture or subculture". Presence of delusion during current or previous episodes was assessed with best estimation procedure taking into account available charts, case notes, and information provided by at least one relative (Leckman et al., 1982). Interviews with the patients were performed using the SCID I interview (Spitzer et al., 1990).Delusional patients were defined on the basis of the presence of delusions in previous episodes, non-delusional patients did not show psychotic symptoms lifetime neither in depression nor in mania. Duration, frequency and type of delusion were not collected.

Severity of depression was rated on the 21-item Hamilton Depression Rating Scale (HDRS). To exclude the potential effect of psychotropic medication load, reflecting the number and dosage of different medications we used a strategy that has been developed for this measurement (Hassel et al., 2008; Phillips et al., 2008). For antidepressants and mood stabilizers, we categorized each medication into low-dose or high-dose groupings, a method validated in brain imaging studies (Sackeim, 2001). We converted antipsychotics to chlorpromazine hydrochloride dose equivalents, coding them as 0 (no medication), 1 (equal to or below the chlorpromazine dose equivalent), or 2 (above the chlorpromazine dose equivalent) relative to the mean effective daily dose of chlorpromazine as defined previously (Davis and Chen, 2004). Benzodiazepine dose was coded as 0, 1, or 2 relative to the midpoint of the recommended daily dose range for each medication recommended in the Physicians' Desk Reference. We generated a composite measure of medication load by summing all individual medication codes for each medication category for each individual participant.

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

Table 1
Clinical and demographic characteristics of the sample divided according to the presence of delusion. Data are means ± S.D.

	Delusion (34)	No delusion (39)	t	p
Age	43.61 ± 10.28	44.05 ± 9.52	0.32	0.64
Education	12.12 ± 4.21	10.35 ± 3.91	−1.98	0.61
Illness duration	28.16 ± 9.85	28.82 ± 9.22	0.37	0.71
Onset	15.73 ± 8.65	16.56 ± 8.67	0.32	0.75
Episodes	6.90 ± 6.21	7.83 ± 7.46	−0.54	0.59
Psychotic episodes	2.57 ± 1.73	–	–	–
Male	23	27	$\chi^2=0.047$	0.83
Hamilton	24.57 ± 5.83	23.50 ± 2.76	0.61	0.55
Medication load	4.29 ± 1.94	4.25 ± 2.22	0.08	0.93

2.2. Image acquisition and post-processing

Brain imaging volumetric T1-weighted sequences were acquired on a 3.0 T scanner (Gyroscan Intera, Philips, Netherlands) using a six channels SENSE head coil using a T-1-weighted magnetization-prepared rapid acquisition with gradient echo (MPRAGE) sequence (TR 25.00 ms, TE 4.6 ms, field of view FOV=230 mm, matrix=256 × 256, in-plane resolution 0.9 × 0.9 mm^2, yielding 220 transversal slices with a thickness of 0.8 mm). Images were 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) and the voxel-based morphometry (VBM) toolbox (VBM8; http://dbm.neuro.uni-jena.de/vbm/) implemented in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/), which combines tissue segmentation, bias correction, and spatial normalization into a unified model. T1-weighted structural images were processed with the "estimate and run" module that uses a maximum a posteriori-method for segment tissue types. Segmented images were normalized to Montreal Neurological Institute (MNI) space using nonlinear DARTEL normalization (Ashburner, 2007). The voxel size for all images was resliced to 1 × 1 × 1 mm^3. Segmented images were then smoothed using a 8-mm full-width at half-maximum (FWHM) isotropic Gaussian kernel.

Group analysis was performed between patients reporting psychotic features during lifetime and patients without history of psychotic features. A two sample t-test was performed in order to investigate volumetric differences between the two groups. Using the Wake Forest PickAtlas software (Wake Forest University, USA; www.fmri.wfubmc.edu), statistical maps were limited to GM and to a priori regions of interest (ROIs) based on previous reports about salience network and executive control (Seeley et al., 2007). The mask included the insula, amygdala, anterior cingulate cortex (ACC) and prefrontal cortex (PFC) (BA 9, 10, and 47). Following a nested hierarchy of tests (Friston et al., 1996), we then tested the set-level significance in this network and to better localize regions showing brain volume differences, we also reported significant areas ($p<0.001$, $K\geq 10$) within the set-level significant ROIs.

We included total intra-cranial volume and months of lithium treatment as covariates to adjust for global atrophy and identify regions with differences that cannot be explained by the total gray matter differences among groups nor by the trophic effect of lithium. Total intra-cranial volume was calculated as the sum of the volumes of gray matter, white matter, and cerebro-spinal fluid, as estimated by the MATLAB get_totals script implemented for SPM (http://www.cs.ucl.ac.uk/staff/g.ridgway/vbm/get_totals.m).

Table 2
Gray matter areas showing a significant effect of delusion. Data are shown for the peak of maximal GM differences in each Broadmann's area (BA): MNI coordinates (x,y,z) of voxels with higher Z values; level of significance.

Cluster size (mm^3)	Signal peak	BA	Region	Z value	P (unc.)
141	36,25,03	47	Inferior frontal gyrus	3.93	<0.000
17	44,03,30	9	Inferior frontal gyrus	3.78	<0.000
83	−30,18,04		Insula	3.55	<0.000
12	40,05,37	9	Middle frontal gyrus	3.46	<0.000