Neuroscience and Biobehavioral Reviews 36 (2012) 2325–2333

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Meta-analysis

Multimodal meta-analysis of structural and functional brain changes in first episode psychosis and the effects of antipsychotic medication

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ARTICLE INFO

Article history:
Received 11 April 2012
Received in revised form 26 June 2012
Accepted 25 July 2012

Keywords:
Antipsychotic
First episode psychosis
Functional magnetic resonance imaging
Meta-analysis
Schizophrenia
Neuroimaging
Voxel-based morphometry
Psychosis

ABSTRACT

Structure and function in the human brain are closely related. At the onset of psychosis, brain imaging studies have identified robust changes in brain function and structure, but no data are available relating these two domains. After systematic literature searches, we included all available studies reporting whole-brain structural or cognitive functional imaging findings in first-episode (FEP) subjects in multimodal Signed Differential Mapping (SDM). Forty-three studies met the inclusion criteria. The structural database comprised 965 FEP subjects matched with 1040 controls whilst the functional cohort included 362 FEP subjects matched with 403 controls. The analysis identified conjoint structural and functional differences in the insula/superior temporal gyrus and the medial frontal/anterior cingulate cortex bilaterally. In these regions, large and robust decreases in grey matter volume were found with either reduced or enhanced activation. Meta-regression analyses indicated that grey matter volume in the anterior cingulate and left insular clusters was influenced by exposure to antipsychotics: patients receiving medication were more likely to show structural abnormalities in these regions.

Contents

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0149-7634
http://dx.doi.org/10.1016/j.neubiorev.2012.07.012

1. Introduction

Neuroimaging studies in early psychosis promise to identify core neurobiological alterations at the onset of the disorder (McGuire et al., 2008; Fusar-Poli et al., 2008). However, despite the impressive growth of functional and structural studies, neuroimaging has yet to become an established as diagnostic, let alone prognostic, instrument in this area, partly as a result of significant heterogeneity across the findings from research studies (Fusar-Poli and Broome, 2006). These inconsistent and conflicting findings may be the result of inter-study differences in sampling methods, sociodemographic and clinical characteristics, and imaging parameters. In addition, recent evidence has indicated that even brief term treatment with antipsychotics can affect both the function (Fusar-Poli et al., 2007a) and the structure (Smieskova et al., 2009) of the brain during the early phase of the disorder.

To address these issues, we previously conducted meta-analyses of structural and functional neuroimaging studies in the early phase of psychosis or in medication-naïve psychotic subjects (Fusar-Poli et al., 2011a, 2007b). Since then, the advent of new tools has allowed researchers to conduct whole-brain meta-analyses employing the spatial coordinates of structural and functional imaging findings and producing neuroanatomical or neurofunctional maps of psychosis onset. In much of this research, there is an implicit assumption that structural abnormalities are linked to functional abnormalities in the brain regions found so affected, or the functional circuits in which they take part. However, this is not necessarily the case since volumetric changes can occur without clear functional correlates, for example as a consequence of nutritional or hydration status, or other confounds (e.g. Weinberger and McClure, 2002), and vice versa. To understand the systems-level neurobiology of first episode psychosis (FEP), it is therefore important to know which brain regions, if any, show conjoint abnormalities in both structure and function. There is some evidence from individual studies indicating that reduction of regional grey matter volume (GMV) is associated with an impaired brain function during cognitive tasks during the ultra high risk (UHR) phase (Fusar-Poli et al., 2011b). Although some individual multimodal studies in early psychosis are available, (Fusar-Poli et al., 2010, 2011c, d, e) this issue is yet to be addressed across multiple studies, using a meta-analytical approach.

To overcome this limitation, we developed a novel voxel-based meta-analytical method to *multimodally* examine the relationship between structural and functional brain abnormalities during FEP. We tested the hypothesis that FEP patients would show both structural and functional alterations in the same brain regions. On the basis of our new multimodal meta-analytical method, we summarized structural and functional findings in a single meta-analytic map, by assessing which brain regions showed *both* structural *and* functional abnormalities in subjects with a FEP. We also controlled our results for a number of potential confounding factors, including exposure to antipsychotics.

2. Methods

2.1. Search strategies

A systematic search strategy was used to identify relevant studies. Two independent researchers (PFP, AC) conducted a two-step literature search. First, a PubMed and Embase search was performed to identify putative studies reporting structural or functional imaging studies in subjects with a FEP. Consistent with the cross-diagnostic approach in the early phases of psychosis, FEP was defined as including both schizophrenia spectrum psychoses (schizophrenia, schizoaffective, schizophreniform) and affective psychoses (bipolar psychosis and psychotic depression) (Fusar-Poli et al., 2012a,b). The search was conducted up to June 2011, with no time span specified for date of publication. The following search terms were used: "psychosis", "schizophrenia", "MRI" (magnetic resonance imaging), "fMRI" (functional MRI), "PET" (positron emission tomography), and "SPECT" (single photon emission computed tomography). In a second step the reference lists of the articles included in the review were manually checked for any studies not identified by the computerized literature search. Although there was no language restriction, all the included papers were in English.

2.2. Selection criteria

Studies were included if they met the following criteria: (a) were reported in an original paper in a peer-reviewed journal, (b) had involved subjects with a FEP and a control group, (c) had employed whole brain structural or functional imaging in both groups. To minimize the heterogeneity of the functional imaging paradigms, only studies employing cognitive tasks were included. Studies not using cognitive paradigms or only reporting region of interests (ROIs) findings were excluded. Similarly, we did not use coordinates relative to analyses employing small volume corrections (SVC) in preselected ROIs. Authors of studies where Talairach or Montreal Neurological Institute (MNI) coordinates (necessary for the voxel-level quantitative meta-analysis) were not explicitly reported were contacted to reduce the possibility of a biased sample set. In cases where the same or similar samples were used in separate papers, we only included data from the analysis of the largest sample. Studies were independently ascertained and checked by the two researchers and inclusion and exclusion criteria were evaluated by consensus. To achieve a high standard of reporting we have adopted 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) guidelines.

2.3. Recorded variables

The recorded variables for each article included in the meta-analysis were: assessment instruments, sample size, gender, mean age of participants, imaging package employed, full width at half maximum (FWHM) of the smoothing kernel, magnet intensity and exposure to antipsychotics. Additionally we recorded the statistical significance of the main findings and the method employed to correct the whole-brain results for multiple comparisons. These data are comprehensively reported in the Supplementary Table S1 to assist the reader in forming an independent view on the following discussion.

2.4. Standard meta-analyses of structural and functional abnormalities

Separate voxel-based meta-analyses of regional GMV and functional brain response abnormalities were conducted with the effect-size version of signed differential mapping (ES-SDM) (Radua and Mataix-Cols, 2009, 2012; Radua et al., 2011), which has been already used to meta-analyze studies on several neuropsychiatric disorders including schizophrenia and bipolar disorder (Bora et al., 2011, 2010; Palaniyappan et al., 2012). This method is based on using the peak coordinates to recreate, for each study, a map of the effect sizes of the differences between patients and controls, and then conducting a standard random-effects variance-weighted meta-analysis in each voxel. Default ES-SDM kernel size and thresholds were used (FWHM = 20 mm, voxel $P = 0.005$, peak height $Z = 1$, cluster extent = 10 voxels) (Radua et al., 2011).

Robustness of the significant results was assessed by means of exploration of the residual heterogeneity, as well as by jack-knife and subgroup analyses. Specifically, we examined the funnel plots

of the peaks of maximum heterogeneity in order to check whether findings might had been driven by few or small noisy studies, or to detect any gross abnormality such as studies reporting opposite results (Radua et al., 2011). As regard to the jack-knife analyses, these consisted of systematically repeating the meta-analyses after excluding one study at a time. Finally, we conducted separate subgroup analyses of those studies using 1.5 Tesla (T) scanners, of those studies using statistical parametric mapping (SPM) software, of those studies using typical smoothing kernels (12 mm in VBM, 8 mm in fMRI), of those studies correcting for multiple comparisons, of those studies where most of the patients were males, and in the functional meta-analysis, of those studies using MRI scanners and of those employing memory tasks.

It must be noted that as we show in Supplementary Fig. S1, patients may have different functional abnormalities which all would be detected as increases of the blood-oxygen-level dependent (BOLD) response, i.e. "patients > controls". In this meta-analysis, we understood differences in that direction as either hyperactivations or failures of deactivation.

2.5. Multimodal analysis of structural and functional response

In order to summarize structural and functional findings in a single meta-analytic map, we assessed which brain regions showed *both* structural *and* functional abnormalities. It must be noted that our analysis did not aim to detect correlations between structural and functional abnormalities, either in the same or different regions – as it could be the case when a structural damage in a given cortical region produces a functional alteration in another brain region. Rather, the aim of this study was to localize those brain regions which display *both* structural *and* functional abnormalities in FEP. It could be, for instance, that some patients present structural but not functional impairment, whilst other patients show functional but not structural impairment. In that case, the meta-analysis should detect both structural and functional impairments, and thus signal the region as multi-modally-affected. This approach is thoroughly described in Radua et al. (in press), and details of the analysis may be found in Supplementary methods SM1.

2.6. Meta-regression analysis

The following variables were explored by means of meta-regression: mean age of the patients, and use of antipsychotic medication (percentages of naïve- and drug-free patients). As in previous meta-analyses, in order to minimize the detection of spurious relationships we decreased the probability threshold to 0.0005, required abnormalities to be detected both in the slope and in one of the extremes of the regressor (e.g. in studies where 0% or where 100% of the patients were receiving medication), and discarded findings in regions other than those detected in the main analyses (Radua and Mataix-Cols, 2009). Finally, regression plots were visually inspected to discard fittings driven by too few studies.

3. Results

3.1. Number of studies found

Forty-three studies met inclusion criteria (Fig. 1). Specifically, in the structural meta-analysis we included 965 FEP subjects (mean age 24, range 15–35 years; 34% females; 76% receiving antipsychotic treatment), matched with 1040 controls (mean age 26, range 15–35 years; 34% females). The cognitive tasks functional imaging cohort included 362 FEP subjects (mean age 26, range 19–36 years; 31% females; 53% receiving antipsychotic treatment), matched with 403 controls (mean age 27, range 23–39 years; 39% females). Cognitive tasks according to the clustering based on the MATRICS domains (Fusar-Poli et al., 2012b) were attention (5), processing speed (1), verbal fluency (5), working memory (6), visual memory (1). All the contrasts included consisted in pairwise comparisons between patients and well-matched controls. The vast majority of the studies included in the meta-analysis recruited healthy subjects in the control group. Details of the included studies are presented in the Supplementary Table S1.

3.2. Changes in regional grey matter volume

Patients with a FEP showed large and robust bilateral decreases of GMV in a peri-Sylvian cluster that included the insula, operculum and the superior temporal gyrus, and in the medial frontal and anterior cingulate cortices (MeF/ACC) (Fig. 2A and Supplementary Table S2). Patients had relatively greater GMV than controls in the right lingual gyrus and left precentral gyrus. The analyses of robustness showed that all these results were highly replicable (Supplementary Table S3).

3.3. Changes in regional brain response to cognitive tasks

Patients with a FEP showed functional abnormalities in the right insula/superior temporal gyrus, as well as in the MeF/ACC. However, the basis of the difference in activation varied within these clusters. In the anterior part of the right insula and in the dorsal ACC there was hypoactivation relative to controls, whereas in the right basal ganglia/thalamus extending to the posterior part of the insula and in the medial frontal cortex, there was a relative reduction in deactivation (Fig. 2B and Supplementary Table S4). Patients also showed reductions in deactivation in the right inferior frontal and left precentral gyri, as well as hypoactivation in left precuneus. Also, a non-significant trend towards functional abnormalities in left insula was observed. The analyses of robustness showed that all these results were highly replicable, with the possible exception of the abnormalities in right inferior frontal gyrus (Supplementary Table S5).

3.4. Multimodal analysis of grey matter volume and brain response

The multimodal analysis showed conjoint abnormalities (large and robust decreases of GMV together with differences in activation/deactivation), in bilateral insulae/superior temporal gyri, as well as in MeF/perigenual ACC. Both the MeF/ACC and insular clusters comprised subregions of hypoactivation and reduced deactivation. Specifically, the anterior parts of the insulae and the dorsal part of the MeF/ACC showed hypoactivation, whereas the posterior parts of the insulae and the ventral part of the MeF/ACC showed reductions in deactivation (Fig. 3 and Table 1).

3.5. Meta-regression

Meta-regression analyses showed that the GMV in MeF/ACC and left insular clusters were significantly more severely decreased in medicated patients (Supplementary Table S6). Indeed, 75% of the studies in which most of the patients were receiving or had received antipsychotic medication reported some GMV decrease around the regression peaks, whilst only 25% of the studies in which most of the patients were drug-naïve or drug-free reported such abnormalities (Fig. 4). However, antipsychotic-naïve patients still showed significant GMV decrease in medial frontal/anterior cingulate cortices and bilateral insula when compared to healthy controls.

Similarly, meta-regression analyses in the functional dataset showed that abnormalities in right insular cluster were more severe in medicated patients (Supplementary Table S7), though these should be taken with caution given the proximity of clusters with

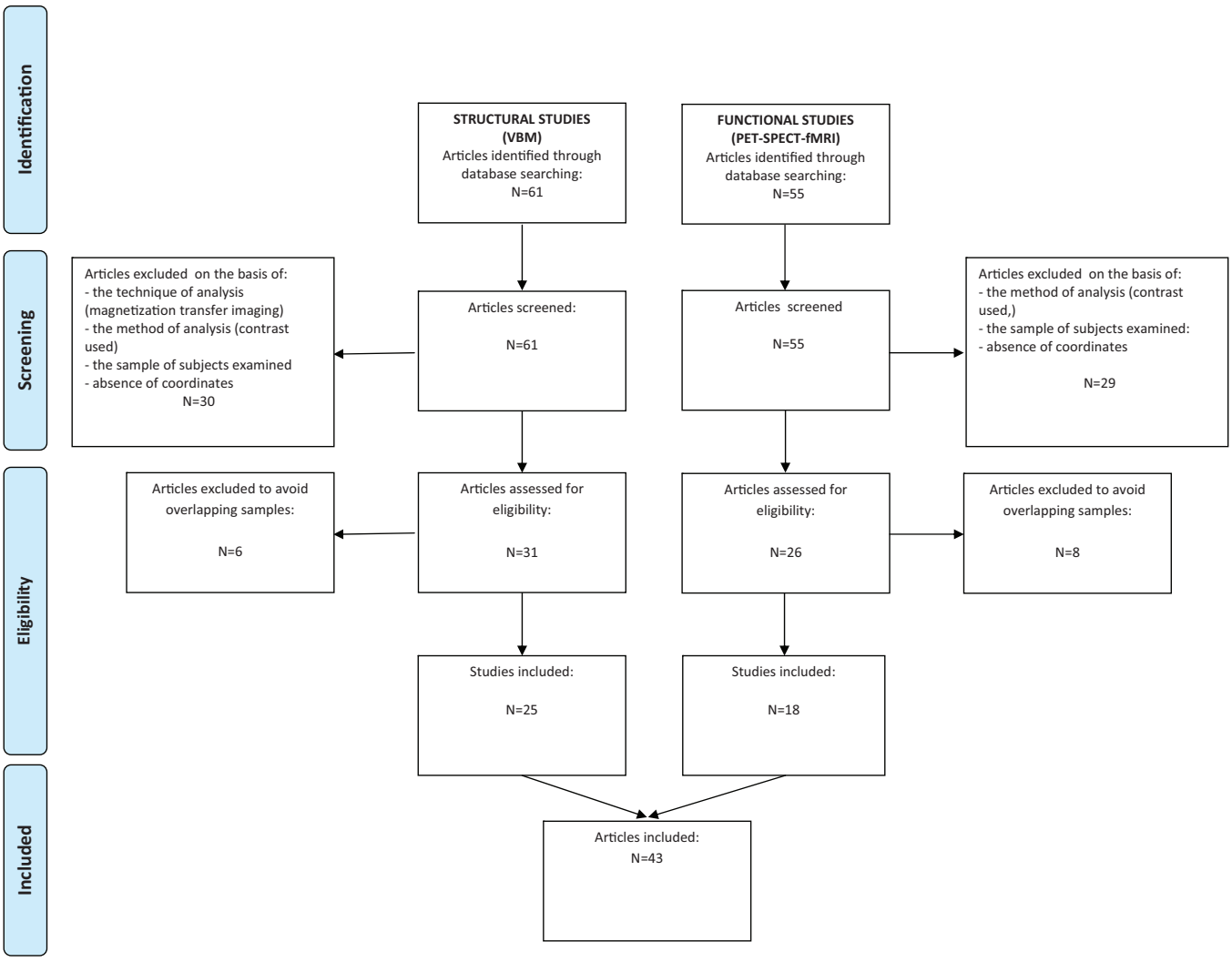

Fig. 1. Diagram of studies included in the present meta-analysis.

opposite findings (hypoactivations vs. hyperactivations/failures of deactivation).

Additional meta-regression findings included a more severe decrease of right insula volume in older patients, and a weaker relationship between younger patients and decreased left insular volume, which was found to be driven by few studies. There were no substantial age differences between medicated and unmedicated samples (medicated patients: 24 years; unmedicated patients: 26 years).

4. Discussion

This is to our knowledge the first multimodal neuroimaging meta-analysis which combines information from whole brain studies investigating GMV and studies investigating the functional brain response to cognitive tasks to more consistently localize the neural substrates of the FEP. To allow colleagues to apply this multimodal meta-analytic technique to study other neuropsychiatric disorders, we have included this function in the SDM software package (http://www.sdmproject.com/).

The main findings of the present study were that patients with a FEP showed decreases in GMV *and* altered brain response in the medial frontal/perigenual anterior cingulate cortices (MeF/ACC) and in bilateral insulae (Fig. 3 and Table 1, raw images available for downloading as Supplementary Images SI1). The changes in functional response were hypoactivations in those subparts of the MeF/ACC and insulae where healthy controls show activations, whilst failures to deactivation in those subparts where healthy controls show deactivations. These results were consistently detected in the several tests which we conducted to assess the robustness of the findings.

Reduction in ACC volume has been observed in psychotic disorders in association with impairments in emotional processing and higher executive functions (for a review see Baiano et al., 2007). The ACC is crucial for integrating cognitive and emotional processes in support of goal-directed behavior. This functional diversity of the ACC, which encompasses executive, social cognitive, affective functions, is in line with our findings of abnormal brain response in the same region, suggesting that alterations in this area may partly explain the difficulties in cognitive and emotional integration that characterize the clinical manifestations of psychosis (Fornito et al., 2009). Very similar subdivisions of anterior pericingulate cortex to that observed here have been obtained through examining the connectivity of this region with amygdala (Pezawas et al., 2005), again pointing to a role of these alterations in emotional regulation. However, the exact implication of this region in human cognition and neuropsychiatry disorders is far more complex extending to the processing of

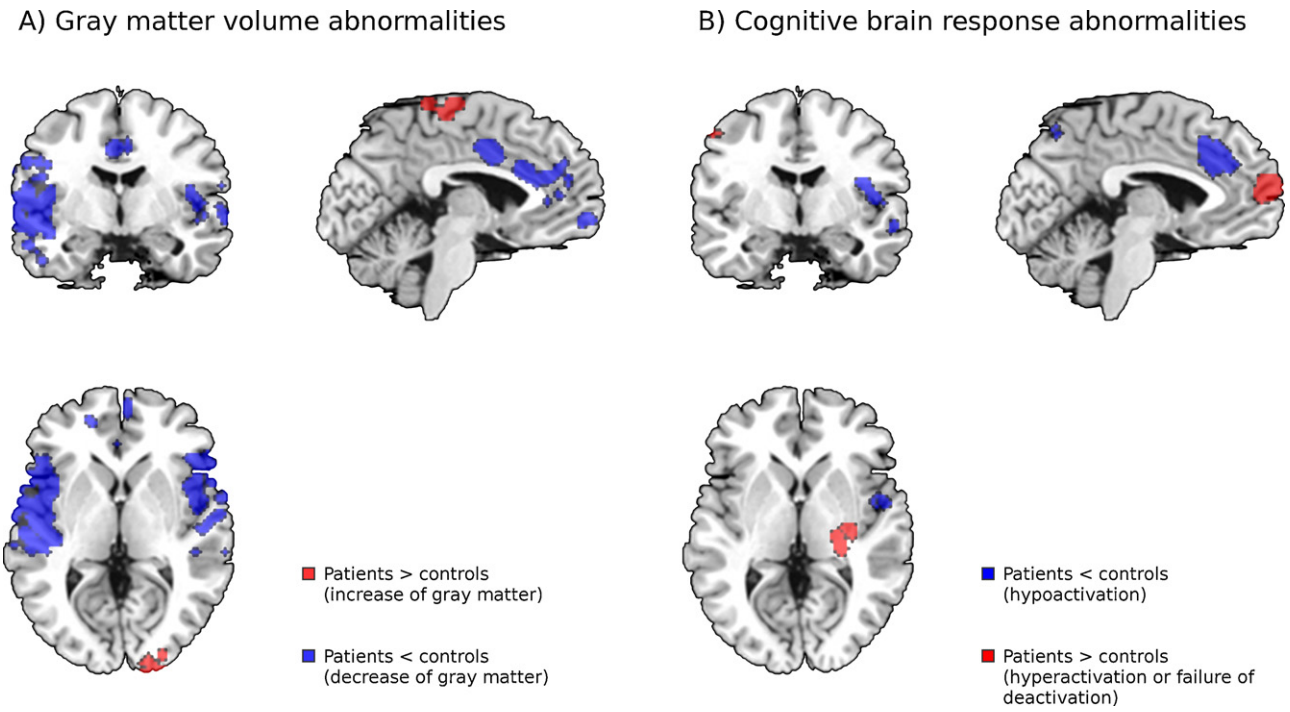

Fig. 2. Separate meta-analyses of structural and functional abnormalities in first psychotic episode.

effects of errors, conflict, error likelihood, volatility, and reward (Alexander and Brown, 2011). The complex neurocognitive profile of MeF/ACC has been recently summarized in a unifying model focusing on a single mechanism, "unexpected non-occurrence", which reflects the negative component of a prediction error signal for both aversive and rewarding events (Alexander and Brown, 2011). Neuropathological research has supported a core role for ACC dysfunction in psychosis revealing alterations in the cellular and synaptic architecture of the region (Todtenkopf et al., 2005).

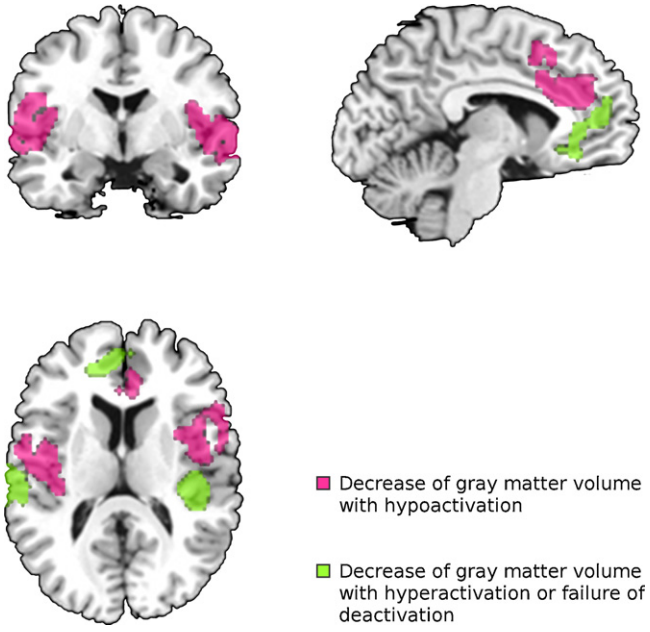

Fig. 3. Multimodal meta-analysis of structural and functional abnormalities in first psychotic episode. The raw image is available for download as Supplementary Images SI1.

A recent SDM voxel-based meta-analysis confirmed ACC (and insular) GMV reductions in subjects presenting a FEP, suggesting that the general salience and emotional regulation network is abnormal from the onset of the illness in schizophrenia (Bora et al., 2011). Our group has previously showed ACC alterations are already

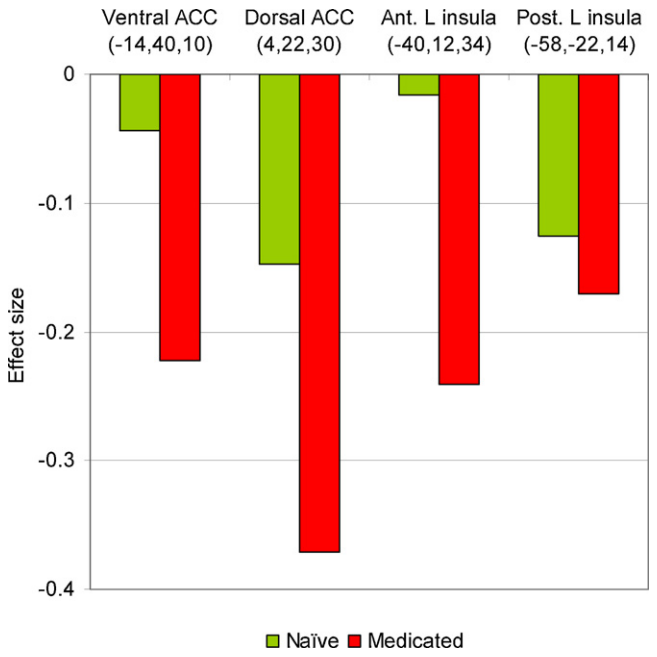

Fig. 4. Effect size of the differences of grey matter volume between antipsychotic-naïve patients and controls (green bars) and between medicated patients and controls (red bars) in the four peaks of multimodal abnormality in anterior cingulated cortex (ACC) and left insula. No differences between naïve and medicated patients were found in right insula (not shown in the plot). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Table 1
Multimodal structural and functional abnormalities in first psychotic episode.

	Talairach coordinates	*P* value[a,b]	No. of voxels[c]	Breakdown (no. of voxels)[c]
Increases of GM + functional abnormalities				
(none)				
Decreases of GM + hypoactivations				
Anterior part of right insula/superior temporal gyrus	42, 0, 12	~0	439	Right BA 22 (136)
				Right BA 13 (112)
				Right BA 44 (47)
				Right BA 21 (38)
				Right BA 6 (35)
				Right BA 9 (31)
				Right BA 38 (13)
	34, 24, 0	0.0001	44	Right BA 47 (26)
				Right BA 13 (10)
Anterior part of left insula/superior temporal/precentral gyrus	−40, 12, 34	~0	407	Left BA 13 (126)
				Left BA 9 (109)
				Left BA 6 (57)
				Left BA 22 (57)
				Left BA 43 (22)
Dorsal part of medial frontal/anterior cingulate gyrus	4, 22, 30	~0	644	Bilateral BA 32 (322)
				Bilateral BA 24 (95)
				Bilateral BA 9 (88)
				Bilateral BA 8 (63)
				Bilateral BA 6 (43)
				Right BA 6 (31)
Decreases of GM + hyperactivations/failures of deactivation				
Posterior part of right insula/superior temporal gyrus	34, 4, −12	~0	71	Right BA 38 (41)
				Right BA 13 (28)
	38, −30, 16	~0	173	Right BA 13 (109)
				Right BA 41 (59)
	50, 20, 10	0.0001	18	Right BA 45 (12)
	56, −16, 32	0.0002	72	Right BA 4 (30)
				Right BA 3 (15)
				Right BA 2 (15)
Posterior part of left superior temporal/postcentral gyrus	−58, −22, 14	0.00005	243	Left BA 42 (106)
				Left BA 40 (66)
				Left BA 41 (27)
				Left BA 22 (25)
				Left BA 43 (11)
Ventral part of medial frontal/anterior cingulate gyrus	−14, 40, 10	0.0001	117	Bilateral BA 32 (38)
				Bilateral BA 10 (31)
				Left BA 9 (27)
				Left BA 24 (17)

[a] Voxel probability threshold: $p = 0.0025$.
[b] Peak height threshold: $p = 0.00025$.
[c] Cluster extent threshold: 10 voxels. Regions with less than 10 voxels are not reported in the cluster breakdown.

evident prior the onset of disease during the prodromal phase and play a crucial role in psychosis transition (Borgwardt et al., 2008). There is also specific functional imaging evidence indicating abnormal ACC engagement in the early phases of psychosis (Boksman et al., 2005; Tan et al., 2005), in subjects at genetic risk for psychosis (Callicott et al., 2003; Whalley et al., 2006) and in subjects at clinical risk for psychosis (Broome et al., 2009) (for a comprehensive review of ACC in emerging psychosis see Rothlisberger et al., 2012).

Similarly, involvement of the insular cortex is a common finding in neuroanatomical studies of schizophrenia. The insula is a cortical structure with extensive connections to many areas of the cortex and limbic system, especially amygdala. It integrates external sensory input with the limbic system and is integral to the awareness of the body's state (interoception) (Wylie and Tregellas, 2010). Many deficits observed in schizophrenia involve these functions and may relate to insula pathology, including the processing of both visual and auditory emotional information, bodily hallucinations and coenaesthesia, altered pain perception, and neuronal representations of the self. Additional evidence confirms that insula alterations are crucial to the development from a high risk state to frank psychosis (Fusar-Poli et al., 2011f; Smieskova et al., 2011; Takahashi et al., 2009) and may be secondary to neurofunctional activation of insular areas during experiencing auditory hallucinations (O'Daly et al., 2007).

However, the ACC and the insula play a crucial role in emotional processing and structural and functional alterations in these areas have been consistently demonstrated in a range of anxiety disorders (Milad et al., 2007; Paulus and Stein, 2006; Radua et al., 2010). Thus, our findings may also represent the neural correlates of the high levels of stress and anxiety that are usually associated with the first onset of frank psychotic symptoms. Of interest, an impact of environmental risk factors linked to social stress, such as urban birth, has recently been shown on the same cingulate subregions identified here (Lederbogen et al., 2011). Furthermore, cingulate–amygdala interactions are altered in genetic variants associated with increased risk of mental illness (although not specifically schizophrenia) in the context of environmental adversity (Pezawas et al., 2005). This interpretation of the findings is consistent with the post-traumatic stress literature suggesting that exposure to traumatic life events is associated with structural abnormalities in various limbic and paralimbic brain regions including the cingulate cortex and the insula, after controlling for genetic factors (Kasai et al., 2008). It is also important to note that

the exact specificity of our findings in relation to the development of schizophreniform vs bipolar disorders is mostly unknown (Yu et al., 2010).

The mechanistic interpretation of our findings is highly speculative. On the one hand, if a region has half the grey matter it should have, it could be that it needed half the baseline blood flow, i.e. assuming that each ml of grey matter needs a fixed amount of blood flow. However, if baseline blood flow is low, a *relative* increase of blood glow may show as an *absolute hypo*-increase of blood flow, and thus as hypo-activation. On the other hand, a reduction of grey matter could also be accompanied by a compensatory hyperfunctionality of the remaining grey matter, which could involve a higher vascularisation and thus even show as hyper-activation. In any case it is important to remember that BOLD fMRI (which is the modality from which the majority of the data we review originates) has no defined zero but contrasts, in the usual approach, two conditions statistically. This means that an activation or deactivation strongly depends on what the comparator condition is. It is, however, noteworthy that our meta-analysis does depict a differentiation between subgenual and supragenual cingulate compartments, and between anterior and posterior insula, indicating that even though there may not be an easily depictable relationship between grey matter and activation in any given condition, across conditions, our meta-analysis identifies functional subdivisions of the structurally abnormal regions that map onto known neuroanatomy and functional circuits. Interpretations are different if we assume the functional damage to appear before the decrease in grey matter. In that case, one could hypothesize that hyperfunctionality may lead to a decrease in grey matter by exhaustion, whilst hypo-functionality may lead to the same situation due to some sort of mechanism to avoid neuronal underemployment.

Schizophrenia is associated with a 14% increase of striatal dopamine synthesis capacity and antipsychotic treatment is the mainstream clinical approach in the field (Fusar-Poli and Meyer-Lindenberg, 2012a, b). Under these premises, we found GMV abnormalities were significantly more severe in medicated patients (Fig. 4). This result is in line with evidence from imaging studies indicating antipsychotic treatment can influence GMV (Ho et al., 2011) and neural activity (Lui et al., 2010) in psychosis. Recent structural imaging studies have further clarified that antipsychotic exposure can affect GMV even at the onset of the disease, in the early phases of psychosis, influencing the structure of temporal and prefrontal cortex (Smieskova et al., 2009). In line with these findings, functional imaging studies have indicated that short-term or acute antipsychotic treatment can alter the europhysiological cortical response during cognitive functioning (Fusar-Poli et al., 2007a). Antipsychotics can reduce frontal cerebral blood flow, and frontal hypoperfusion could be a mechanism underlying smaller brain tissue volumes (Ho et al., 2011). The differences we detected can reflect long-lasting changes in brain volume caused by antipsychotic medication but also compensatory processes associated with the underlying disease process. Although we showed a consistent effect of antipsychotic medication in these areas it did not account for the whole magnitude of GMV alterations. Our data therefore support a model in which antipsychotics target regions of key pathology in early psychosis, but do not necessarily suggest that drug treatment causes these alterations. Indeed, about 25% of the studies in which most of the patients were drug-naïve reported abnormalities in the same brain regions. Our recent voxel-based meta-analysis of VBM studies in drug-naïve subjects at high clinical risk for psychosis or with a confirmed psychosis onset was also associated with GMV decreases in temporo-insular and ACC regions (Fusar-Poli et al., 2011f). However, it cannot be fully ruled out that antipsychotic medications may cause some of the observed alterations (Knowles et al., 2010). Of interest, ACC function and structure has been reported to be especially sensitive to remedial antipsychotic treatment in psychosis (Lahti et al., 2009; Stip et al., 2009). As there is evidence indicating that few weeks of antipsychotic treatment modulate the ACC response (Lahti et al., 2004; Snitz et al., 2005), the question of the functional significance of dynamic prefrontal changes in the first phases of psychosis may have some potential clinical implications for early interventions.

This study has some limitations. First, whilst voxel-wise meta-analytical methods provide excellent control for false positive results, it is more difficult to avoid false negative results (Radua et al., 2011). We cannot therefore exclude the possibility that we were unable to detect some group differences because of limited statistical power. Indeed, this could be the case for the separate meta-analysis of functional abnormalities, where a lower number of studies could be included and insular/temporal abnormalities only reached statistical significance in the right hemisphere. Second, some of the included VBM studies reported grey matter density rather than volume. Grey matter density might be understood as a type of GMV that has not been corrected by the distorting effects of the normalisation to the stereotactic space; therefore, its inclusion in the meta-analysis is valid (it is also a "volume") although it could add a source of heterogeneity. Other methodological differences such as the use of one or another smoothing kernel (see Supplementary Table S1) may further contribute to this heterogeneity. Third, the included functional imaging studies had employed different cognitive tasks to evoke the brain response of interest, which could result in a source of heterogeneity. However, we excluded studies not employing cognitive paradigms in order to minimize this heterogeneity, and a separate subgroup analysis of only those studies employing memory tasks yielded nearly identical results. In fact, our finding that insula and MeF/ACC were found to be consistently functionally abnormal in FEP is especially remarkable given that the employed tasks have little or no emotional component and do not primarily activate these particular structures. The results may therefore have been quite different if a salience processing task, or an emotional faces task had been used to provide the fMRI data. Fourth, the meaning of GMV alterations in the adolescent and young adult's is unclear and may have been confounded by factors including other medication types as antidepressants, consumption of alcohol, tobacco or illicit drugs as cannabis, and socioeconomic status. Fifth, we cannot discard that the medication effects could be confounded by factors such as duration and severity of psychosis, socioeconomic status or neurocognitive variables. Unfortunately, only few studies reported these data, preventing a covariate analysis. Similarly, only few studies reported the actual medication doses, for what a meta-regression with chlorpromazine equivalents was not feasible. It is also possible that the greater abnormalities in medicated patients could be related to a selection bias of relatively well patients able to be scanned without treatment. Sixth, we did not aim to detect correlations between structural and functional abnormalities, but rather, to localize those brain regions in which the disorder is associated with both structural and functional abnormalities. Future studies are encouraged in order to investigate the spatial and temporal relationships between the structure and function of the regions detected in this meta-analysis. Finally, our criterion of conjoint functional and structural abnormalities is stringent and regions with meta-analytic support for either functional or structural changes in early psychosis, but not both, should still be considered in the pathophysiology of the illness.

5. Conclusions

Results from our multimodal meta-analysis demonstrate a close relationship between structural and functional brain alterations in subjects with a first episode of psychosis. In the medial

frontal/anterior cingulate cortices, and in the bilateral insulae, patients showed a decrease in grey matter volume as well as abnormal functional response. Some of these changes may be partially related to treatment with antipsychotic medication.

Conflict of interest

The authors declare no conflict of interest in relation to the present manuscript.

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.neubiorev.2012.07.012.

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