



## Review

## Neuroanatomy of vulnerability to psychosis: A voxel-based meta-analysis

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## ARTICLE INFO

## Article history:

Received 10 August 2010

Received in revised form 7 December 2010

Accepted 10 December 2010

## Keywords:

VBM  
Psychosis  
High risk  
MRI  
Preventive psychiatry

## ABSTRACT

**Background:** Individual structural imaging studies in the pre-psychotic phases deliver contrasting findings and are unable to definitively characterize the neuroanatomical correlates of an increased liability to psychosis and to predict transition to psychosis.

**Method:** Nineteen voxel-based morphometry (VBM) studies of subjects at enhanced risk for psychosis and healthy controls were included in an activation likelihood estimation (ALE) meta-analysis.

**Results:** The overall sample consisted of 701 controls and 896 high risk subjects. Subjects at high risk for psychosis showed reduced gray matter (GM) volume as compared to controls in the right superior temporal gyrus, left precuneus, left medial frontal gyrus, right middle frontal gyrus, bilateral parahippocampal/hippocampal regions and bilateral anterior cingulate. High risk subjects who later developed a psychotic episode showed baseline GM volume reductions in the right inferior frontal gyrus and in the right superior temporal gyrus.

**Conclusions:** GM volume reductions in temporo-parietal, bilateral prefrontal and limbic cortex are neuroanatomical correlates of an enhanced vulnerability to psychosis. Baseline GM reductions in superior temporal and inferior frontal areas are associated with later transition to psychosis.

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## 1. Introduction

Recent advances in psychiatric research have allowed clinicians to assess and diagnose individuals during the early phases of psychosis, prior to the onset of frank disease, in studies of those at high-risk state for psychosis (for review see Riecher-Rossler et al., 2006). To investigate the enhanced vulnerability to psychosis two high-risk research paradigms have been employed in the current literature (Cannon, 2005). Endorsing the genetic high-risk approach, putative endophenotypes can be evaluated for association with genetic risk for psychosis by comparing the unaffected co-twins or the unaffected relatives of patients with healthy controls (Johnstone et al., 2000; Whalley et al., 2007). The alternative approach focuses on individuals who are considered to be at increased clinical risk because of the presence of an intermediate illness phenotype such as subclinical psychotic symptoms (Cornblatt et al., 2002; McGlashan, 1998; Yung et al., 1998). High risk subjects present attenuated positive (ideas of reference, magical thinking, perceptual disturbance, paranoid ideation, odd thinking and speech) (Yung et al., 2005) and negative (Lencz et al., 2004; Riecher-Rossler et al., 2009) symptoms which do not reach the psychosis threshold, in association with subtle neurocognitive deficits (Brewer et al., 2005, 2006; Eastvold et al., 2007; Hawkins et al., 2008; Lencz et al., 2006; Pukrop et al., 2006; Riecher-Rossler et al., 2009; Simon et al., 2007) and psychosocial impairment (Fusar-Poli et al., 2009). Compared to healthy persons, they have a significantly greater probability of developing the illness within the following months (Yung et al., 2008). While some of the high risk subjects will subsequently develop psychosis, others will continue to experience subthreshold symptoms but will not become psychotic. To improve the predictive value of an early diagnosis there is an urgent need of reliable neurophysiological markers that underlie an increased liability to psychosis and those which denote that transition to frank psychosis is likely.

Over the past two decades, neuroimaging techniques have been extensively employed to address the functional and structural correlates of the early phases of psychosis. Structural neuroimaging studies (sMRI) during first episode psychosis indicate reductions in regional gray matter (GM) volumes at initial presentation and volume loss over time in those patients who have a deteriorating clinical course (Ho et al., 2003; Lieberman et al., 2001). There is also a significant body of MRI findings reporting structural abnormalities in the pre-psychotic phases. Most of these studies have been cross-sectional (Lawrie et al., 2008; Wood et al., 2008) and aimed to demonstrate that structural changes found in patients with schizophrenia would also be identified before onset, based on the dominant neurodevelopmental theory of the disorder. This traditional model proposes that abnormalities in fetal brain development during early stages of neuronal selection and migration are the principal reasons for failure of brain functions in early adulthood. Specifically, studies in high risk samples have shown that structural abnormalities in the frontal, temporal and limbic cortices may predate the illness onset (Borgwardt et al., 2007b; Meisenzahl et al., 2008; Pantelis et al., 2003) (for a systematic review of structural imaging studies in high risk subjects see Wood et al., 2008). However these individual imaging studies have produced contrasting findings and are unable to

definitively characterize which brain regions are associated with an increased liability to psychosis. In particular, methodological factors such as different imaging and analysis methods (Fusar-Poli et al., 2010a) may be a source of heterogeneity across studies (Fusar-Poli et al., 2008a). For example, MRI studies employing pre-defined regions of interests (ROIs) are challenging because targets for quantification in ROI are mainly located in the prefrontal and temporal cortex and thus are likely to affect the analysis sensitivity and alter the overall picture of the imaging results. Another major limitation is the small sample size and the associated low statistical power of most MRI studies. Furthermore, the modulatory effect of factors such as type of risk (genetic/clinical), age of high risk subjects, differences in ascertainment strategies or short-term treatment with atypical antipsychotic has not been adequately addressed. In addition, as the high risk state is a dynamic condition, the onset and the time-course of structural alterations are currently unknown. In particular, to sustain preventive interventions it seems critical to clarify the neurobiological predictors of a transition from a high-risk state to full-blown psychosis.

To address such heterogeneity we conducted a meta-analysis of voxel-based-morphometry (VBM) studies in high risk subjects and matched controls. VBM is a modern automated whole-brain magnetic resonance image measurement technique which allows investigations of focal differences in brain structure by using statistical parametric and non-parametric mapping. In our meta-analysis, VBM high-risk studies were analyzed by employing the activation likelihood estimation (ALE) method. Until techniques such as ALE became available, it has not been possible to integrate data from voxel-based studies of psychosis into meta-analyses. In coordinate-based meta-analyses such the ALE, brain coordinates reported from independently performed imaging experiments are analyzed in search of areas that are relevant for the investigated contrast (Neumann et al., 2008). The ALE approach is currently one of the most powerful and reliable meta-analytical methods in neuroimaging and offers consistent advantages over other meta-analytical approaches. Despite some meta-analyses of structural findings in chronic schizophrenia (Ellison-Wright et al., 2008; Honea et al., 2005; Wright et al., 2000) or first episode subjects (Chan et al., 2011; Ellison-Wright et al., 2008; Kempton et al., 2010; Vita et al., 2006), no comprehensive voxel-level meta-analyses of MRI studies in the pre-psychotic phases in subjects aged from childhood to later adulthood are available to date. In addition, no meta-analysis has addressed the modulatory effect of clinical (i.e. genetic vs clinical risk for psychosis, effect of antipsychotic treatment) or imaging factors on the structural findings (Chan et al., 2011).

The principal aim of the study was to examine the neuroanatomical correlates of vulnerability to psychosis by comparing MRI findings between subjects at enhanced risk (HR) and controls using an un-biased whole brain approach. The second aim was to characterize the baseline structural abnormalities predicting a subsequent transition to psychosis by comparing high-risk subjects with (HR-T) and without (HR-NT) later transition to psychosis. Finally, we tested the putative modulating effect of imaging factors, genetic/clinical risk, age, and antipsychotic exposure.

**Table 1**  
VBM studies of subjects at enhanced risk for psychosis included in the voxel-based meta-analysis.

Author	Year	Psychosis Risk	N controls	% Females C	Age C	N HR	% Females HR	Age HR	T	VBM method	FWHM	Antipsychotic treatment
Fusar-Poli (Fusar-Poli et al., 2010b)	2010	Clinical	15	40%	25	15	47%	24	1.5	SPM5	8	Y
Fusar-Poli (Fusar-Poli et al., 2010c)	2010	Clinical <sup>2</sup>	41	19%	26	39	38%	24	1.5	SPM5	8	Y
Borgwardt (Borgwardt et al., 2009)	2009	Genetic	34	29%	39	9	33%	34	1.5	SPM2	8	N
Jacobson (Jacobson et al., 2010)	2009	Clinical	14	79%	11	11	64%	12	3	FSL	4.2	N
Koutsouleris (Koutsouleris et al., 2009)	2009	Clinical	75	39%	25	46	37%	25	1.5	SPM5	10	N
Lui (Lui et al., 2009)	2009	Genetic	10	60%	43	10	50%	41	3	SPM2	8	N
Stone (Stone et al., 2009)	2009	Clinical	27	52%	25	27	48%	25	3	SPM5	8	Y
Borgwardt (Borgwardt et al., 2008)	2008	Clinical <sup>2</sup>				20	40%	25	1.5	SPM5	5	Y
Honea (Honea et al., 2008)	2008	Genetic	212	51%	33	213	58%	36	1.5	SPM2	10	N
Meisenzahl (Meisenzahl et al., 2008)	2008	Clinical	75	39%	25	40	38%	25	1.5	SPM5	10	N
Borgwardt (Borgwardt et al., 2007b)	2007	Clinical	22	41%	23	35	37%	24	1.5	SPM2	5	Y
Borgwardt (Borgwardt et al., 2007a)	2007	Clinical <sup>1</sup>	22	41%	23	12	25%	25	1.5	SPM2	5	Y
Hulshoff Pol (Hulshoff Pol et al., 2006)	2006	Genetic	44	50%	35	22	50%	37	1.5	?	4	N
Job (Job et al., 2005)	2005	Genetic <sup>2</sup>	19	37%	21	65	48%	21	1	SPM99	12	N
McDonald (McDonald et al., 2004)	2004	Genetic <sup>3</sup>				36	61%	48	1.5	SPM99	8	N
McIntosh (McIntosh et al., 2004)	2004	Genetic	49	53%	35	26	46%	34	1.5	SPM99	8	N
Job (Job et al., 2003)	2003	Genetic	36	53%	21	146	49%	21	1	SPM99	8	N
Marcelis (Marcelis et al., 2003)	2003	Genetic	27	56%	35	32	56%	35	1.5	BAMM	4.2	N
Pantelis (Pantelis et al., 2003)	2003	Clinical <sup>2</sup>				75	43%	20	?	?	?	Y

1: HR transition; 2: the HR group was divided in HR-T and HR-NT; 3: the comparison group is established psychosis only; Y: yes; N: no; ?: unknown.

## 2. Materials and methods

### 2.1. Studies election

A systematic search strategy was used to identify relevant studies. Two independent researchers conducted a two-step literature search. First, we carried out a Medline search in the English-language literature to identify putative sMRI studies employing computational techniques that had reported data on subjects at high risk for psychosis. The search was conducted between February and April 2010, and no time span was specified for date of publication. We used the following keywords

MRI, VBM, prodromal psychosis, genetic risk to psychosis, clinical risk to psychosis. To qualify for inclusion in the review, studies must have: (1) been an original paper appeared in a peer-reviewed journal; (2) have analyzed MRI data with voxel-based morphometry (VBM) in subjects at high risk for psychosis (clinical or genetic risk, see below); (3) have provided standard Talairach or Montreal Neurologic Institute (MNI) coordinates, necessary for a voxel-level quantitative meta-analysis (Laird et al., 2005a; Turkeltaub et al., 2002). Studies reporting only region of interests (ROIs) findings without whole-brain analyses were not included in the present meta-analysis. In a second step the reference lists of the articles included in the review were additionally checked for relevant studies not identified by computerized literature searching. Finally, authors of studies where Talairach or MNI coordinates were not explicitly reported were contacted to reduce the possibility of a biased sample set. Studies were independently ascertained and checked by the two researchers and inclusion and exclusion criteria were evaluated by consensus. Table 1 lists the articles included in the meta-analysis. In order to assist the reader in forming an independent view of the results, meta-analytical data such as mean sample age, gender composition of sample, field strength, image analysis package, exposure to antipsychotics were collected across all studies.

### 2.2. Voxel-based meta-analysis

Meta-analyses were carried out using the activation likelihood estimation technique (Turkeltaub et al., 2002) implemented in GingerALE ([www.brainmap.org/ale/](http://www.brainmap.org/ale/)). Meta-analyses were performed using the Talairach stereotactic coordinates derived from the studies listed in Table 1. Because the Talairach system is defined such that left is negative, coordinates based on the radiological convention were transformed. In addition, the spatial normalization template was determined for each study and all foci reported in MNI space were converted to Talairach space by using the foci conversion option available in the software used for the meta-analytical procedure. The Brett transform has previously been used to convert MNI coordinates to Talairach space (Brett et al., 2001). However, recent findings show that MNI/Talairach coordinate bias associated with reference frame (position and orientation) and scale (brain size) can be substantially reduced using the best-fit MNI to Talairach transform (Lancaster et al., 2007). This transform has been validated and shown to provide improved fit over the Brett MNI to Talairach transform (Brett et al., 2001). The Talairach atlas was used to identify the anatomical landmarks of the activation results. Meta-analyses were performed when at least two studies providing coordinates suitable for meta-analysis were available. Although the explanation of the results depends on the size of meta-analysis and there are no community-accepted criteria for the results, for a study of this size, if 6 or more foci contribute to a cluster, it is considered very robust, and if 3–5 foci contribute to a cluster, it is acceptable (see the forum of GingerALE, <http://www.brainmap.org/forum/>) (Li et al., 2009). The equally weighted coordinates were used to form estimates of the activation likelihood for each voxel in the brain as

described by Turkeltaub et al. (2002). In brief, to allow for error in spatial localization related to inter-subject variation in functional anatomy and inter-study differences in data smoothing and registration, the reported loci of maximal activation were modelled as the peaks of 3D Gaussian probability density functions with full-width half-maximum (FWHM) of 10 mm. The probabilities of each voxel in standard space representing each primary locus of activation were combined to form a map of the ALE score at each voxel. Statistical significance was assessed using a permutation test with 5000 permutations, corrected for multiple comparisons (the false discovery rate (FDR) was set at  $P=0.001$ ). Clusters of suprathreshold voxels exceeding 300 mm<sup>3</sup> in volume were defined as loci of brain activation in common across all studies included in the meta-analysis (Laird et al., 2005a). The resultant ALE maps were thresholded at  $p=0.005$ , in line with previous studies (Ellison-Wright et al., 2008).

Different meta-analyses were conducted on the database. In the main analysis we contrasted all subjects at high risk for psychosis versus controls (HR vs control). To clarify the trait or state value of the identified neuroanatomical abnormalities we contrasted HR subjects who developed a psychotic episode over time (HR-T) versus HR subjects who did not transit to psychosis (HR-NT). We then compared brain structure in the pre-psychotic and full established psychosis (HR vs psychosis). To discriminate the differential correlates of genetic and clinical risk we conducted separate contrasts between these groups (genetic HR vs controls, clinical HR vs controls, genetic HR vs clinical HR). Finally, to investigate the potential confounding effect of magnet field, age and antipsychotic treatment, meta-analytic comparisons between subgroups of coordinates (magnet  $\geq 3$  T vs magnet  $\leq 1.5$  T, treated vs untreated, age < sample median vs age > sample median) were carried out by using the permutation test described in more detail by Laird et al. (2005a), after controlling that there were no significant differences in the number of coordinates found in each group. The overall meta-analytical approach (Laird et al., 2005a) has been widely used in a number of studies (Chikazoe et al., 2007; Dickstein et al., 2006; Ellison-Wright et al., 2008; McMillan et al., 2007; Owen et al., 2005; Witt et al., 2008). Whole-brain maps of the ALE values were imported into MRIcron software program ([www.sph.sc.edu/comd/rorden/mricron](http://www.sph.sc.edu/comd/rorden/mricron)) and overlaid onto the brain template for presentation purposes.

### 3. Results

#### 3.1. Number of studies found

Nineteen studies met inclusion criteria for the current study for a total of 277 foci. The overall sample was relative to a cohort of 705 controls (mean age = 27.59, SD = 7.94) and 896 high risk subjects (mean age = 28, SD = 8.47). The sample included 10 clinical high risk studies and 9 genetic high risk studies (Diagram 1). The majority of studies were performed on a 1.5 T MRI scanner and employed SPM as imaging package. Exposure to antipsychotic treatment across all studies is reported in Table 1.

#### 3.2. Inclusion criteria for subjects at high-risk for psychosis in individual studies

The neuroimaging studies included different high-risk samples (Fusar-Poli et al., 2008b): (a) genetic high-risk subjects including monozygotic and dizygotic twins discordant for schizophrenia (non-psychotic twin) or relatives (first or second degree) of patients affected with psychosis (b) clinical high-risk subjects according to different inclusion criteria (*Comprehensive Assessment of the At Risk Mental State*, “CAARMS”; *Structured Interview for Prodromal*

*Symptoms*, “SIPS”; *Bonn Scale for Assessment of Basic Symptoms*, “BSBPS”; *Basel Screening Instrument for Psychosis*, “BSIP”). Two well established centers from the English-speaking area – Personal Assessment and Crisis Evaluation clinic (PACE) in Melbourne and Outreach And Support In South London clinic (OASIS) in London – have used the instrument called *Comprehensive Assessment of Symptoms and History* (CAARMS) (Yung et al., 2005) to assess the attenuated psychotic symptoms (APS), brief limited psychotic symptoms (BLIPS) and trait + state risk factor (Yung et al., 1998) in the high-risk population. The same criteria with the newly developed shorter *Basel Screening Instrument for Psychosis* (BSIP) (Riecher-Rossler et al., 2007, 2008) were assessed in Basel in the *Early Detection of Psychosis Clinic* (FEPSY). The German research network on schizophrenia (GRNS) in Bonn, Düsseldorf, Cologne and Munich employed the *ERIRAOs* (Maurer and Hafner, 2007) – *Early Recognition Inventory* based on *Interview for the Retrospective Assessment of the Onset of Schizophrenia* (IRAOS) (Hafner et al., 1992) and *Bonn Scale for Assessment of Basic Symptoms* (BSABS) (Klosterkotter et al., 2001). The North American Prodrome Study employed the *Structured Interview for Prodromal Symptoms* (Cannon et al., 2008) to address psychopathological features characterizing an impending psychosis. Conversely, studies enrolling subjects affected with schizotypal personality disorder, which is characterized, like schizophrenia, by positive or psychotic-like symptoms and negative or deficit-like symptoms (Siever and Davis, 2004) were not included in the meta-analysis as the transition rate to psychosis in this group is still under discussion (Bedwell and Donnelly, 2005).

Although the risk for psychosis in genetic/clinical high-risk samples is significantly higher than in the general population, it is not the same across these different groups: monozygotic twins have a 40–50% concordance rate for the illness over lifetime (Tsuang et al., 2002), first-degree relatives of schizophrenia patients have approximately a 10-fold increased risk for later illness compared to non-relatives over lifetime (Chang et al., 2002), while in clinical high-risk cohorts the probability to develop psychosis ranges from 25% within three years (BSAPS) (Velthorst et al., 2009), up to 35% within 2.5 years (SIPS) (Cannon et al., 2008), 25% after two years (BSIP) (Riecher-Rossler et al., 2007) and 41% within two years (ARMS) (Yung et al., 2003, 2007).

#### 3.3. Voxel based meta analyses

##### 3.3.1. Neuroanatomical abnormalities reflecting an increased risk for psychosis

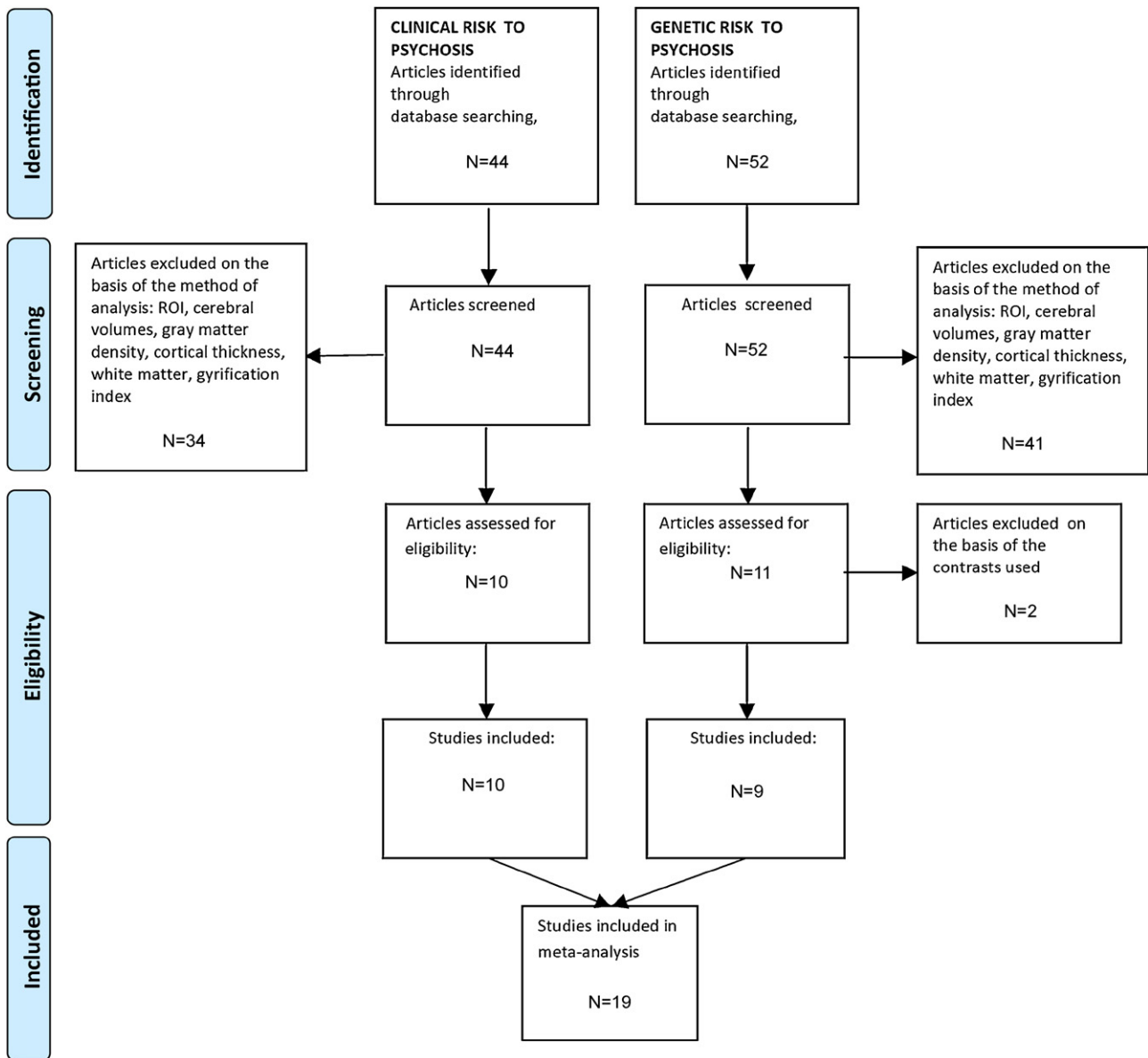
Across all studies, subjects at risk for psychosis showed reduced gray matter (GM) volume as compared to controls in temporal (right superior temporal gyrus) and parietal regions (left pre-cuneus), in the prefrontal cortex bilaterally (left medial frontal gyrus and right middle frontal gyrus) and in limbic regions (bilateral parahippocampal/hippocampal regions, bilateral anterior cingulate, Fig. 1) (Table 2). No regions of increased GM volume in the high risk group as compared to controls were detected.

##### 3.3.2. Neuroanatomical correlates of transition to psychosis

Within the clinical high risk group, subjects who developed a psychotic episode over time (HR-T) showed reduced GM in a cluster spanning the right inferior frontal gyrus and the right insula and in the right superior temporal gyrus as compared to high risk subject who did not develop a psychotic episode (HR-NT) (Table 2, Fig. 2). Conversely, there were no significant GM increases in subject who developed a psychotic episode as compared to subjects who did not become psychotic.

##### 3.3.3. High risk for psychosis vs established psychosis

When subjects at enhanced risk to psychosis were compared to subjects with established psychosis, GM abnormalities were



**Diagram 1.** Diagram illustrating identification, screening and selection of articles included in the meta-analysis.

detected in the amygdala bilaterally, in the left prefrontal (medial frontal gyrus), and temporal (middle temporal gyrus) cortex and in the right parietal cortex (precuneus). In these brain regions subjects at risk for psychosis showed increased GM volume as compared to subject with established disease (Table 2 and Fig. 3).

### 3.3.4. Neuroanatomical abnormalities reflecting a genetic high risk for psychosis

Subjects at enhanced genetic risk for psychosis showed reduced GM volume in the left parahippocampal gyrus and in the anterior cingulate bilaterally (Table 2 and Fig. 4) as compared to controls. No GM increases were observed in the high risk group as compared to controls.

### 3.3.5. Neuroanatomical abnormalities reflecting a clinical high risk

Subjects at enhanced clinical risk for psychosis showed reduced GM volume in the left hippocampus, insula and in the right superior temporal gyrus and in the right prefrontal cortex (inferior frontal gyrus, medial frontal gyrus) (Table 2 and Fig. 4) as compared to

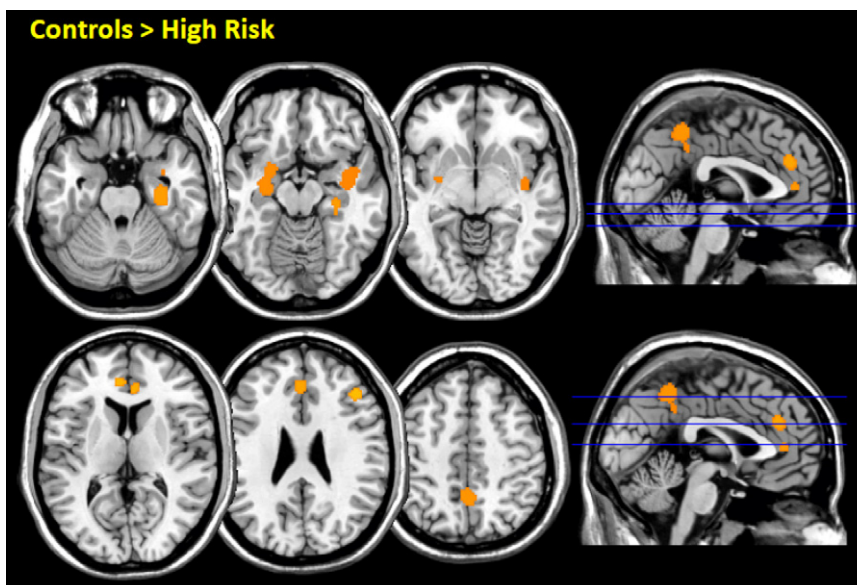
controls. No GM increases were observed in the high risk group as compared to controls.

### 3.3.6. Genetic risk versus clinical risk

Individuals at enhanced clinical risk for psychosis showed gray matter reduction in the bilateral anterior cingulate when compared with subjects at enhanced genetic risk for psychosis. Conversely, subjects at genetic risk for psychosis showed gray matter reductions in the left hippocampus and insula and in the right superior temporal gyrus when compared to subjects at clinical risk for psychosis (Table 2).

### 3.3.7. Confounding factors

High risk subjects who had received atypical antipsychotic treatment showed GM increases in a cluster spanning the right inferior frontal gyrus and the right insula ( $x=34$ ,  $y=18$ ,  $z=-6$ , volume=528 mm<sup>3</sup>, ALE value 0.015312, Fig. 5) as compared to antipsychotic-naïve high risk subjects. Older high risk subjects (age > 25 years) showed reduced GM volume in the left anterior cingulate ( $X=-2$ ,  $y=44$ ,  $z=10$ , volume=972 mm<sup>3</sup>,



**Fig. 1.** GM abnormalities in subjects at high risk for psychosis as compared to controls. Regional GM decreases in subjects at enhanced risk for psychosis as compared to controls.

**Table 2**  
Neuroanatomical correlates of increased liability to psychosis.

Brain region	Side	BA	Site of max ALE			Vol (mm <sup>3</sup> )	Max ALE value
			x	y	z		
<b>Controls &gt; high risk</b>							
Superior temporal gyrus	R	21	46	−4	−6	2208	0.0170
Parahippocampal gyrus	L	34	−22	4	−16	1904	0.0130
Precuneus	L	7	0	−50	52	1824	0.0172
Parahippocampal gyrus	R	36	32	−22	−20	1592	0.0156
Medial frontal gyrus	L	9	0	38	26	576	0.0098
Anterior cingulate	R	32	8	36	14	504	0.0117
Anterior cingulate	L	32	−6	42	8	360	0.0108
Middle frontal gyrus	R	9	42	32	26	360	0.0122
<b>Controls &gt; clinical high risk</b>							
Parahippocampal gyrus	L	Hip	−26	−12	−14	1256	0.0122
Superior temporal gyrus	R	38	32	4	−28	640	0.0070
Insula	L	13	−40	−28	16	608	0.0075
Inferior frontal gyrus	R	47	16	18	−16	316	0.0063
Medial frontal gyrus	R	11	0	32	−14	316	0.0065
<b>High risk without transition &gt; high risk with transition</b>							
Inferior frontal gyrus	R	47	34	18	−6	1256	0.0100
Superior temporal gyrus	R	22	50	4	−2	600	0.0072
<b>Controls &gt; genetic high risk</b>							
Parahippocampal gyrus	L	34	−22	4	−16	744	0.0119
Anterior cingulate	R	32	−6	42	8	680	0.0108
Anterior cingulate	R	24	2	30	14	328	0.0070
<b>Genetic high risk &gt; clinical high risk</b>							
Anterior cingulate	L	32	−6	42	8	832	0.0112
Anterior cingulate	R	24	2	30	14	816	0.0069
<b>Clinical high risk &gt; genetic high risk</b>							
Parahippocampal gyrus	L	Hip	−26	−12	−14	1072	0.0121
Insula	L	13	−40	−28	16	504	0.0074
Superior temporal gyrus	R	38	32	4	−28	456	0.0070
<b>High risk &gt; schizophrenia</b>							
Parahippocampal gyrus	R	Amy	26	−8	−24	2048	0.0158
Parahippocampal gyrus	L	Amy	−20	−4	−18	1168	0.0154
Medial frontal gyrus	L	10	0	46	12	968	0.0124
Middle temporal gyrus	L	22	−60	−46	4	736	0.0103
Precuneus	R	7	2	−42	46	600	0.0111

FDR = 0.01, cluster  $p < 0.005$ ; Amy, amygdala; Hip, hippocampus; BA, Brodmann area; ALE, activation likelihood estimation.

ALE value = 0.02415) as compared to younger high risk subjects (age < 25 years). No GM increases were observed in the older high risk subjects as compared to the younger ones. A significant effect for FWHM was detected in the amygdala ( $x = -25$ ,  $y = -4$ ,  $z = -20$ , volume = 402 mm<sup>3</sup>, ALE value = 0.019567), while no effects for magnet field strength were detected.

#### 4. Discussion

The present study aimed at addressing the neuroanatomical correlates of an increased liability to psychosis. High risk subjects showed reduced GM volume in temporal, parietal and prefrontal cortex and in limbic regions as compared to controls. Gray mat-

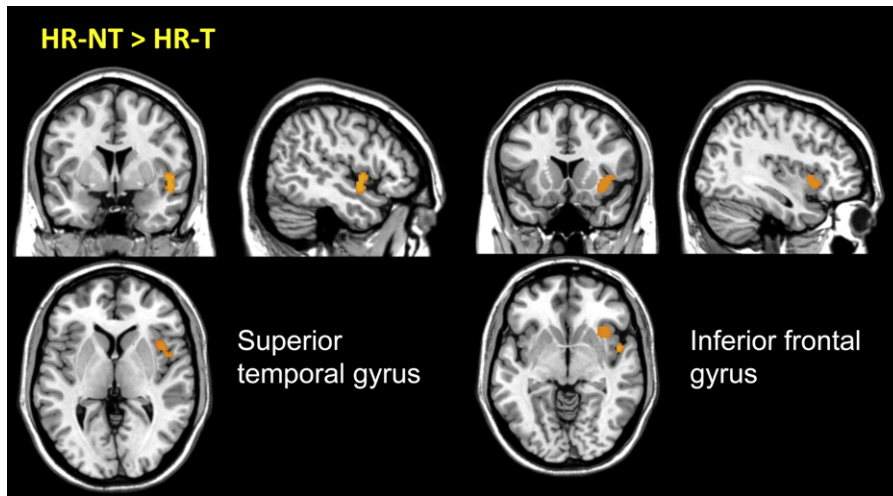


Fig. 2. GM reductions in the frontal and temporal cortex associated with transition to psychosis (HR-NT > HR-T).

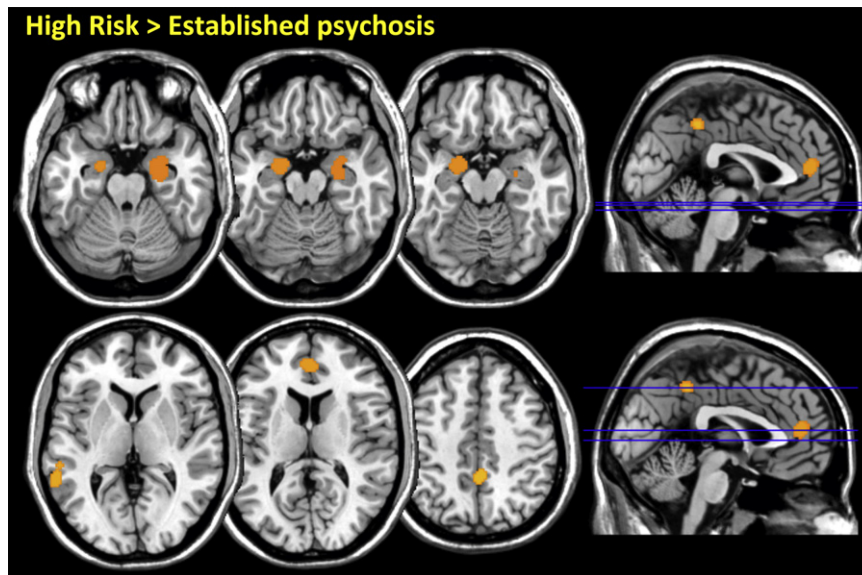


Fig. 3. GM abnormalities in subjects at risk for psychosis as compared to subjects with an established psychosis (HR > psychosis). HR-T, subjects at high risk for psychosis who later developed the disease; HR-NT, subjects at high risk for psychosis who later did not develop the disease.

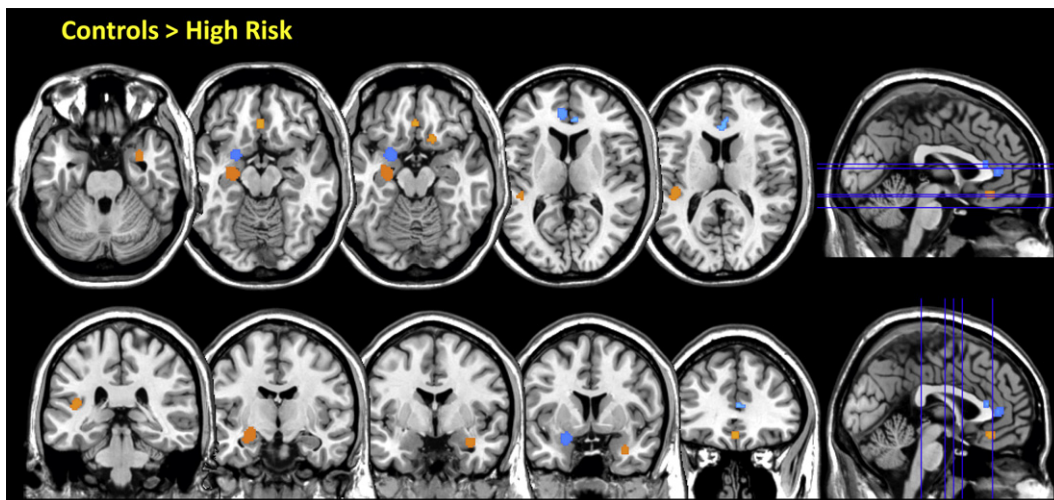
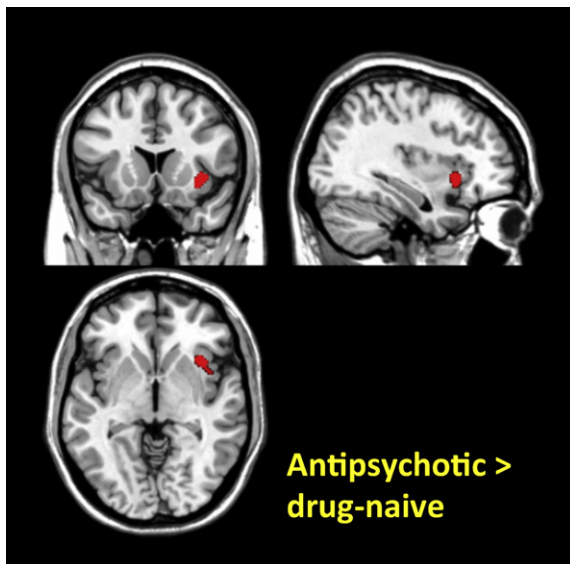


Fig. 4. Neuroanatomical correlates of genetic (blue) and clinical (yellow) enhanced risk for psychosis (controls > HR). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)



**Fig. 5.** Antipsychotic effects on prefrontal GM volume in subjects at enhanced risk for psychosis (treated with antipsychotic > untreated).

ter reductions in prefrontal and temporal areas at baseline were associated with later transition to psychosis. Atypical antipsychotic treatment had a significant effect on prefrontal regions.

We adopted a multiple-step approach with the encompassing objective of reducing heterogeneity across MRI findings and providing reliable neuroanatomical markers of an enhanced risk to psychosis. At the stage of study selection we decided to include whole-brain studies only (VBM studies) avoiding region of interest (ROI) studies in the light of the profound methodological differences of the two methods. We employed ALE methods in a large sample relating to 896 high risk subjects and to 277 foci. As recent ALE meta-analyses have been published with significant smaller samples and less than 10 foci (Li et al., 2009), our results are particularly robust. We have chosen a voxel-location statistical approach (voxel-based, ALE) in place of the standard effect-size meta-analysis, to definitively ascertain the location of brain abnormalities in the pre-psychotic phases (Murphy et al., 2003). Specifically, ALE assumes that although each study reports the specific coordinates of the GM alterations, issues such as inter subject variability in brain anatomy and differences in investigators' labels for anatomical regions may lead to some uncertainty as to the actual locations of these abnormalities. In fact, one of the difficulties when comparing imaging studies is that there is considerable variability when labeling neuroanatomical regions, and differences in nomenclature could obscure findings. An advantage of the ALE technique is that because it uses the coordinates of reported foci (rather than anatomical labels) for meta-analysis, it avoids the problem of any mislabeling of regions in the primary literature (Laird et al., 2005b). A further benefit is that the exclusion of negative data has very little effect on the results (Murphy et al., 2003).

Our first aim was to provide reliable neuroanatomical maps of enhanced risk for psychosis by comparing the high risk group with the control group. We found a pattern towards GM reductions in subjects at high risk for psychosis, with volume loss within the bilateral prefrontal (medial/middle frontal gyri) and bilateral limbic cortex (parahippocampal/hippocampal regions and anterior cingulate) and within the temporo-parietal cortex (left precuneus and right superior temporal gyrus). Although single studies reported gray matter increases in the high risk subjects as compared to controls (Borgwardt et al., 2007a; Honea et al., 2008; Jacobson et al., 2010) no significant results were found in the meta-analysis, in

line with previous ALE studies suggesting a trend towards gray matter loss in clinical groups as compared to healthy volunteers (Chan et al., 2011). Such alterations are not attributable to effects of the illness or its treatment. As the high risk group had an enhanced risk of developing a psychotic disorder but were not psychotic, our findings can be interpreted as a neural correlate of an increased vulnerability to psychosis. Alterations in the prefrontal structure and function are a core feature of psychotic disorders (for a review see Tan et al., 2009) and represent the preferential target of action of atypical antipsychotic drugs (Artigas, 2010). Hippocampal/parahippocampal dysfunction is a robust and frequently replicated finding in psychotic disorders, with alterations in both the structure and function of this region (Achim and Lepage, 2005; Vita et al., 2006), thought to underlie the memory impairments that are evident at the behavioural level (for a review see Boyer et al., 2007; Preston et al., 2005). Reduction in anterior cingulate volume has been observed in psychotic disorders in association with impairments in emotional processing and higher executive performances (for a review see Baiano et al., 2007). Alterations in the superior temporal gyrus and its subregions have been shown in psychosis and appear to be involved in the generation of hallucinations and thought disorders (for a review see Sun et al., 2009). Finally, the precuneus, with its wide-spread connectivity with both cortical and subcortical structures, is involved in self-centred mental imagery strategies, and episodic memory retrieval, functions which have been shown to be impaired in psychosis (for a review see Cavanna and Trimble, 2006). All the above brain regions are similar to those found to be abnormal in functional magnetic resonance imaging studies of high risk subjects. Abnormalities in the functional response of prefrontal (Broome et al., 2008; Morey et al., 2005), temporal (Crossley et al., 2009; Seidman et al., 2003) and parietal (Broome et al., 2008) cortex of high risk subjects can underlie the observed neurocognitive impairment (for a meta-analysis of functional imaging studies in the clinical or genetic high-risk group see Fusar-Poli et al., 2007b; MacDonald et al., 2009). These findings suggest that functional and structural abnormalities in the high risk group may share a common pathophysiology. In a recent VBM-fMRI study we have confirmed that in high risk subjects, reduced prefrontal activation during working memory was associated with GM reductions in the same area (Fusar-Poli et al., 2010b). Of interest, when the high risk subjects were compared to subjects with established psychosis, GM abnormalities were confirmed in limbic (amygdala), prefrontal (medial frontal gyrus), and temporo-parietal cortices (middle temporal gyrus and precuneus). Such findings corroborate the hypothesis that the structural brain abnormalities in the high risk status resemble those observed during the clinical expression of psychosis but are less marked. Such theory is in line with evidence from functional imaging studies indicating that the neurofunctional abnormalities during cognitive tasks are qualitatively similar but less severe in high risk subjects as compared to first episode patients (Fusar-Poli et al., 2007b).

The second aim of the present study was to assess the neurobiological predictors of transition from a high-risk state to full-blown psychosis. We thus compared brain structure in high risk subjects with or without later transition to psychosis. We found greater GM retraction at baseline in those who go on to make a transition to psychosis in the right inferior frontal gyrus and superior temporal gyrus. Such alterations can be interpreted as neurobiological predictors of psychosis transitions. In a recent review of longitudinal (whole brain or region of interest) imaging studies, our group has confirmed that psychosis onset is associated with progressive structural and neurochemical abnormalities in prefrontal and temporal cortices (Smieskova et al., 2010). It is interesting to note that the first VBM study examining GM volume of high risk with or without transition to psychosis already found reduced volume in lateral temporal and inferior frontal cortex at baseline

(Pantelis et al., 2003). The superior temporal gyrus contains several important structures of the brain, including primary auditory cortex in Heschl's gyrus and auditory association cortical areas in the anterior portion of planum temporale (Sun et al., 2009). The latter regions have been thought of as candidates for the neural basis of language-related psychotic symptoms such as auditory hallucinations and thought disorders in patients with schizophrenia (Allen et al., 2008; Yamasaki et al., 2007). Similarly, previous literature has suggested an important role for the inferior frontal gyrus, in the pathophysiology of schizophrenia (Suga et al., 2009). Volume reduction in the inferior frontal gyrus has been associated with severe psychotic symptoms such as delusional behaviour and severity of positive or negative psychotic symptoms (Suga et al., 2009). Given the above link between superior temporal and inferior frontal alterations and intense psychotic symptoms our finding of GM retractions in these areas may underlie the clinical onset of full-blown psychotic symptoms. Overall, our meta-analysis added evidence to the available literature by showing that baseline structural abnormalities in superior temporal gyrus and inferior frontal gyrus might be most predictive for a development of full-blown psychotic symptoms. GM volume deficits in individuals at-risk for psychosis indicate that structural abnormalities are present, at least in part, before the onset of the illness and are likely to be linked to disruption of normal brain developmental processes. As our database included participants with ages ranging from childhood to later adulthood, the observed structural alterations may reflect a disruption of normal brain developmental processes. The developing brains of 11–13-year old children has been shown mainly right lateralized prefrontal-temporal dysfunction, focal GM volume abnormalities and white matter microstructural reductions that are associated with the risk phenotype (Jacobson et al., 2010). In addition, our meta-analysis is the first to show that the genetic or clinical level of high risk for psychosis is not directly comparable. In fact we found that clinical high risk groups have gray matter reductions in the anterior cingulate and gray matter increases in the hippocampus, temporal gyrus and insula as compared to genetic high risk groups. These gray matter alterations reflect the differential load of genetic or psychopathological factors in the pre-psychotic phases and may represent neuroanatomical correlates of heterogeneity across high risk groups.

In addition, we have shown atypical antipsychotic treatment is associated with GM increases in the right inferior frontal gyrus. Previous structural imaging studies have indicated that antipsychotic treatment in early phases of psychosis may alter GM volume in temporal and prefrontal cortex (Smieskova et al., 2009) while functional imaging studies have indicated that even a short term antipsychotic treatment can alter the cortical response during cognitive tasks (Fusar-Poli et al., 2007a). However there are different effects of first and second generation antipsychotics, with neuroprotective GM increase after few weeks of treatment with an atypical, but not typical, antipsychotic (Garver et al., 2005; Lieberman et al., 2005). As subjects included in the present meta-analysis had been mainly treated with atypical medications, our finding of increased GM in the inferior frontal gyrus is in line with the above evidence. Furthermore, as we have observed GM retractions in the inferior frontal gyrus in association with transition to psychosis it is possible to speculate that antipsychotic treatment can reverse such alterations and prevent the psychosis onset.

Limitations of the current study are well acknowledged. Although the VBM provides an unbiased approach to establish the presence of regional differences in gray matter by surveying the whole brain, some limitations must be acknowledged. Limitations of VBM methods relate to the difficulty of spatially normalising brains, the robustness of standard parametric tests and the interpretation of the results (Mechelli et al., 2005). In particular, VBM is sensitive to systematic shape differences attributable to misreg-

istration from the spatial normalisation procedure (Mechelli et al., 2005). Although the quantitative meta-analytic method employed here represents a significant advance for integrating multi-site neuroimaging data, the approach remains subject to the basic limitation of literature reviews, in particular the “file drawer” problem. However, a benefit of ALE meta-analyses is that the exclusion of negative data has very little effect on the results (Murphy et al., 2003). In addition, the present method did not allow for weighting of the results based on the level of statistical significance reported in each study. This means that we cannot exactly determine the relative strengths of GM differences. Because the data were collected cross-sectionally, we cannot determine at what stage the observed neuroanatomical differences were first evident. This issue could be addressed by longitudinal neuroimaging studies of subjects at different time points within the HR population. A further limitation was that there was not enough statistical power to compare different clinical high risk groups (i.e. ARMS vs SIPS) or different genetic high risk groups (i.e. first degree relatives vs twins). In addition, because of heterogeneity of assessment instruments employed across studies it was not possible to correlated gray matter abnormalities with psychopathological measures. Finally, although we have attempted to address the effect of age, exposure to antipsychotic, image analysis and field strength of magnet, other factors such as substance abuse, gender and cognitive functioning could potentially increase heterogeneity across studies.

## 5. Conclusions

Structural alterations in bilateral prefrontal and limbic cortex and in temporo-parietal cortex are neuroanatomical correlates of an increased vulnerability to psychosis. High risk subjects who later become psychotic show additional volumetric reductions in superior temporal and inferior frontal areas relative to those who do not. Changes in these areas may be crucial to the development of psychotic illness. The present voxel-based meta-analysis suggest that it may in future be possible to the use structural MRI to facilitate the prediction of psychosis.

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