Research Paper

Voxel-wise meta-analysis of fMRI studies in patients at clinical high risk for psychosis

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Background: Reliable neurofunctional markers of increased vulnerability to psychosis are needed to improve the predictive value of psychosis risk syndrome and inform preventive interventions. **Methods:** I performed a signed differential mapping (SDM) voxel-wise meta-analysis of functional magnetic resonance imaging (fMRI) studies of patients at clinical high risk for psychosis. **Results:** Ten studies were included in the analysis. Compared with controls, high-risk patients showed reduced neural activation in the left inferior frontal gyrus (Brodmann area [BA] 9) and in a cluster spanning the bilateral medial frontal gyrus (BA 8,6), bilateral superior frontal gyrus (BA 8,6) and the left anterior cingulate (BA 32). There was no publication bias. Heterogeneity across studies was low. Sensitivity analysis confirmed the robustness of the findings. **Limitations:** The cross-sectional nature of the included studies prevented the comparison of high-risk patients who later experienced a psychotic episode with those who did not. Other caveats are reflected in methodologic heterogeneity across tasks employed by different individual imaging studies. **Conclusion:** Reduced neurofunctional activation in prefrontal regions may represent a neurophysiologic correlate of increased vulnerability to psychosis.

Introduction

Over the past decade, research on psychosis risk syndrome (also known as "clinical high risk," "ultra high risk" or "prodromal" syndrome) has progressed exponentially, allowing for preventive interventions to be feasible in clinical psychiatry.[1] In light of the severe functional, social and economic long-term impact of psychoses, preventive interventions have been welcomed with enthusiasm, and the number of new clinical services devoted to people at enhanced clinical risk for psychosis has grown worldwide. Ultimately, such clinical and research interests have led to proposed inclusion of high-risk syndrome as a new diagnosis in the upcoming DSM-V.[2–4] However, despite these developments, the validity of high risk criteria is still greatly discussed, and the problem of false-positive results undermines the benefits of preventive interventions. Thus there is an urgent need for reliable neurobiologic markers underlying the transition from a risk state to established psychosis. Neuroimaging techniques have been used to address this issue,[5] and high risk for psychosis has been associated with alterations in the structure,[6,7] function,[8–10] connectivity[11] and neurochemistry[12–14] of the brain[5,15] (for a review or structural findings see Fusar-Poli and colleagues,[6] and for reviews of functional findings see Smieskova and colleagues[8] and Fusar-Poli and colleagues[9]). However, despite the advancements of basic research in neuroscientific investigations, the diagnosis of the high-risk state is still based on pure psychopathologic criteria[16] because of inconsistent and conflicting findings across individual imaging studies.[15] My group conducted some years ago what we believe was the first meta-analysis of structural and functional neuroimaging studies in patients at high risk for psychosis.[9] However, to our knowledge, no comprehensive voxel-based meta-analysis has ever addressed the robustness of neurofunctional findings in patients at clinical risk for psychosis. The present study reviews functional magnetic resonance imaging (fMRI) studies involving patients at enhanced clinical risk for psychosis by adopting a relatively new voxel-based meta-analytic tool that allows the results for sample sizes of individual studies to be weighted and controlled for several moderator variables, including sociodemographic, clinical and imaging factors.

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Methods

Selection procedures

Search strategies

First, I performed a MEDLINE search to identify putative fMRI studies involving patients at clinical high risk for psychosis. The search was conducted in February 2011, and no time span was specified for the date of publication. I used the following search terms: "fMRI," "psychosis risk" and "prodromal psychosis." Second, the reference lists of the articles retrieved were manually checked for relevant studies not identified by computerized literature searching.

Selection criteria

To be included in this meta-analysis, the studies must have

- been an original paper published in a peer-reviewed journal,
- enrolled a group of patients at enhanced clinical risk for psychosis according to established criteria (see below) and a matched control group, and
- employed whole-brain fMRI methods.

Studies reporting only regions of interest (ROIs)[17] findings were not included. Authors of studies in which 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. After contacting the authors, no methodologic ambiguities remained regarding the design or analysis of any of the studies. In cases where the same or similar samples were used in separate papers, I included data from the analysis of only the largest sample. To achieve a high standard of reporting, I followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18]

Recorded variables

The recorded variables for each article included in the meta-analysis were the psychometric instrument employed to assess the enhanced risk for psychosis, sample size, sex, mean age of participants, imaging package and field intensity. In addition, I recorded the statistical significance of the main findings and the method employed to correct the whole-brain results for multiple comparisons. Results are comprehensively reported in tables.

Voxel-wise meta-analysis

Prior to conducting the voxel-based meta-analysis, I applied a strict selection of the reported peak coordinates of functional differences: only those that appeared statistically significant at the whole-brain level were included. I also carefully checked that the same statistical threshold throughout the whole brain was used within each included study to avoid biases toward liberally thresholded brain regions because it is not uncommon in neuroimaging studies for the statistical threshold for some ROIs to be more liberal than for the rest of the brain.

I converted MNI coordinates to Talairach space using the Lancaster transformation, which has been shown to be more exact than the Brett method. In cases when the authors of a study had converted their MNI coordinates to the Talairach space using the Brett method, I first converted the coordinates back to MNI space (using the Brett method) and subsequently converted them to Talairach space using the Lancaster transformation.

I used signed differential mapping (SDM) to analyze neurofunctional changes in patients at clinical high risk for psychosis (www.sdmproject.com/software/).[19,20] The SDM methods have been described in detail elsewhere[20] and are only briefly summarized here. Once the coordinates are selected and converted, a map of the neurofunctional differences is separately recreated for each study. This consists of assigning a value to the voxels close to each of the reported coordinates within a map (based on the Talairach Daemon). Signed differential mapping uses a 25-mm full-width at half-maximum unnormalized Gaussian kernel. This kernel is adapted from that of activation likelihood estimation,[21] and it is preferred to that of multilevel kernel density analysis (MKDA)[22] because it assigns a higher value to the voxels closer to the reported coordinates.[20] When a voxel can be assigned values from more than 1 coordinate in the same study, these values are summed. An important downside of the sum of values is a bias toward studies reporting various coordinates in close proximity, as voxels can achieve rather large values. Multilevel kernel density analysis elegantly overcomes this problem by limiting the values within 1 study to a maximum, and SDM also incorporates this feature. A novelty of the method used in this study is that both positive and negative coordinates are reconstructed in the same map, resulting in an SDM.[20] This is an important feature that prevents a particular voxel from erroneously appearing to be positive (i.e., increased activation) and negative (i.e., decreased activation) at the same time. Once an individual SDM has been created for each study, a meta-analytic SDM is calculated. It must be noted that individual SDMs do not account for variability within each study, therefore the usual meta-analytic calculations are not applicable. However, MKDA overcomes this issue by defining the meta-analytic value of a voxel as the proportion of studies reporting a coordinate around the voxel (weighted by the square root of the sample size of each study so that studies with larger samples contribute more). Finally, a null distribution of the meta-analytic values is created to test which voxels have more studies reporting differences of activation around them than expected by chance. This is performed by means of Monte Carlo randomizations of the location of the coordinates.[20] The null distribution is generated at the whole-brain level to maximize statistical stability with relatively reduced computation time (almost 40 million values are obtained with 500 randomizations).

Statistical analysis

Age, percentage of female patients, imaging package[23] and magnet intensity were entered as covariates in meta regression analyses. The age of patients was included in its linear and quadratic forms (age and age squared, the latter obtained

from age mean and variance), as the developmental trajectories of some brain regions during prodromal psychosis may be nonlinear. Results were then thresholded at $p < 0.001$, uncorrected, which has been found to be empirically equivalent to $p < 0.05$, corrected, for multiple comparisons under different conditions.[19] Additionally, I applied an extent threshold of Ke > 20 voxels. These analyses were complemented with additional analyses to assess the robustness of the findings.[20] These additional analyses included descriptive analyses of quartiles to find the actual proportion of studies reporting results in a particular brain region (regardless of p values) and jackknife sensitivity analyses to assess the replicability of the results. Heterogeneity among studies was assessed with the Q statistic, with magnitude of heterogeneity being evaluated with the I^2 index.[24] Publication bias was examined by visually inspecting funnel plots and applying the regression intercept of Egger and colleagues.[25]

Results

Ten studies satisfied the inclusion criteria for the current meta-analysis. Patients at clinical high risk for psychosis and controls were matched with respect to age and sex ($p > 0.05$). Most studies were performed on a 1.5-T MRI scanner and employed SPM as an imaging package. Most of them reported whole-brain findings, corrected for multiple comparisons (Table 1).

Inclusion criteria for patients at enhanced clinical risk for psychosis

Prodromal psychotic symptoms in patients at high clinical risk for psychosis may present as "attenuated psychotic symptoms" (APS)[38] that are present below the threshold of full psychosis, "brief and self-limiting psychotic symptoms" (BLIPS),[38] a significant decrease in functioning in the context of a "genetic risk for schizophrenia" (GDR),[38] or as early subjective disturbances of cognitive processes and the perception of the self and the world ("basic symptoms").[39] Different interview measures have been developed to operationalize the high-risk criteria: the Comprehensive Assessment for the At-Risk Mental State,[36] the Structured Interview for Prodromal Symptoms[37] and the Bonn Scale for the Assessment of Basic Symptoms.[35] In a recent meta-analysis, my group has shown that belonging to one of these groups confers an enhanced risk of a psychotic episode developing over a relatively short period of time, with transition rates of 18% after 6 months of follow-up, 22% after 1 year, 29% after 2 years and 36% after 3 years.[40]

Voxel-wise meta-analysis

There was a consistent pattern toward reduced blood oxygen level–dependent response independent of tasks employed in high-risk patients (Fig. 1). Compared with controls, the high-risk patients showed reduced neural activation in the left inferior frontal gyrus (Brodmann area [BA] 9) and in a cluster spanning the bilateral medial frontal gyrus (BA 8,6), bilateral superior frontal gyrus (BA 8,6) and the left anterior cingulate (BA 32; Table 2). Conversely, no significant increases in neural activation were observed in the high-risk group compared with the control group (31 foci).

Sensitivity analysis and descriptive analysis of quartiles

Reduction of activation in the left medial frontal gyrus and inferior frontal gyrus were detected in the median analysis, meaning that most of the studies had found some degree of decreased neurofunctional activation in these regions. Whole-brain jackknife sensitivity analysis showed that the functional differences in the left medial frontal and inferior frontal gyri were highly replicable, as these findings were preserved throughout all 11 combinations of 10 studies. No additional significant clusters were found in any of the study combinations.

Table 1: Functional magnetic resonance imaging studies involving patients at clinical high risk for psychosis included in the meta-analysis

			Control			High-risk						
Study	Year	High-risk assessment	No.	% female	Age, yr	No.	% female	Age, yr	Tesla	fMRI method	Statistical threshold	Task
Brüne et al.[26]	2011	SIPS+BSABS	26	34	29	10	30	26	1.5	SPM5	Unc	Theory of mind
Fusar-Poli et al.[27]	2010	CAARMS	15	46	25	15	40	24	1.5	SPM5	FWE	Paired associate learning
Allen et al.[28]	2010	CAARMS	15	46	26	15	40	27	1.5	SPM2	Corr	Sentence completion task
Sabb et al.[29]	2010	SIPS	24	50	19	43	40	18	3	FSL	Corr	Language processing
Pauly et al.[30]	2010	CAARMS	12	17	24	12	17	24	1.5	SPM2	Monte Carlo	*N*-back
Broome et al.[31]	2010	CAARMS	15	30	25	17	30	24	1.5	XBAM	FDR	Random movement generation
Allen et al.[32]	2009	CAARMS	22	36	28	18	44	27	1.5	SPM2	FWE	False memory task
Broome et al.[10]	2009	CAARMS	15	30	25	17	30	24	1.5	XBAM	FDR	Verbal fluency, *n*-back
Benetti et al.[33]	2009	CAARMS	14	36	26	16	38	24	1.5	SPM5	FWE	Delayed match to sample
Seiferth et al.[34]	2008	SIPS	12	17	25	12	17	25	1.5	SPM2	FWE	Emotional faces

BSABS = Bonn Scale for Assessment of Basic Symptoms;[35] CAARMS = Comprehensive Assessment for the At-Risk Mental State;[36] corr = corrected for multiple comparisons; FDR = false discovery rate; fMRI = functional magnetic resonance imaging; FWE = family-wise error; SIPS = Structured Interview for Prodromal Symptoms;[37] unc = uncorrected for multiple comparisons.

Effect of moderators

There were no significant effects for age, sex, magnet intensity and imaging package on the above meta-analytic findings.

Publication bias, heterogeneity and sensitivity

Visual inspection of funnel plots revealed no obvious evidence of publication bias. Quantitative evaluation of publication bias, as measured by the Egger intercept, was nonsignificant ($p = 0.24$). According to the criteria set by Higgins and Thompson,[41] heterogeneity in published studies was small in magnitude and statistically nonsignificant (Q = 11.258, $p = 0.54$, $I^2 = 7.286$). Jackknife sensitivity analysis confirmed the robustness of these findings.

Discussion

The present voxel-wise meta-analysis has addressed the neurofunctional alterations in patients at enhanced risk for psychosis. I found consistent evidence across different task modalities for a reduced prefrontal activation in high-risk patients compared with controls.

I opted to use SDM, as this method allows weighting the results for sample sizes and addressing the confounding effect of moderators. I found significant neurofunctional alterations in prefrontal regions of the high-risk patients across different task modalities; however, these results should be interpreted cautiously, as I have included both cognitive and emotional processes. These fMRI paradigms are well known to recruit different cortical areas, such as the prefrontal cortex, subserving executive and working memory functioning, and the temporo-limbic network, subserving emotional processing. On the other hand, the differential engagement of cognitive and affective brain areas has been questioned by recent advancements in cognitive neurosciences. For example, in a large voxel-based meta-analysis of fMRI studies employing emotional faces stimuli, my group showed that emotional processing was not only associated with increased activation in a number of visual, limbic and temporoparietal areas, but also in prefrontal areas, such as the inferior frontal and the medial frontal gyri.[42] Some brain areas, such as the anterior cingulate, have extensive anatomic connections to both dorsolateral prefrontal cortex and subcortical areas and are implicated not only in response selection, error detection and memory, but also in social cognition and emotional processing.[22] In line with these findings, the present study's sensitivity analysis and quartile description confirmed that the neurofunctional activations detected in the prefrontal areas were observable in most of the studies, regardless of the fMRI task used. Specifically, patients at risk for psychosis showed reduced activation in the inferior frontal gyrus and in a wide cluster spanning the medial frontal gyrus, the superior frontal gyrus and the anterior cingulate compared with healthy controls. These neurophysiologic differences could reflect an increased vulnerability to the later development of frank psychosis.

The inferior frontal gyrus plays a crucial role in language production and has been widely implicated in prodromal psychosis. A recent positron emission tomography–fMRI study involving high-risk patients and matched controls[12] has shown a direct relation between altered neurofunctional activation in the inferior frontal gyrus and subcortical elevation of presynaptic striatal dopamine (DA).[43] The correlation was specific to the high-risk patients, suggesting that the observed relation was related to pathophysiologic changes associated with an increased vulnerability to psychosis. Activity in dopaminergic terminals within the striatum may be controlled by the inferior frontal gyrus, which may act as a "brake" on the striatal DA system. Alternatively, striatal hyperdopaminergia can influence activity in the inferior frontal gyrus and impair neurocognitive function. There is also evidence suggesting that the normalization of the abnormal

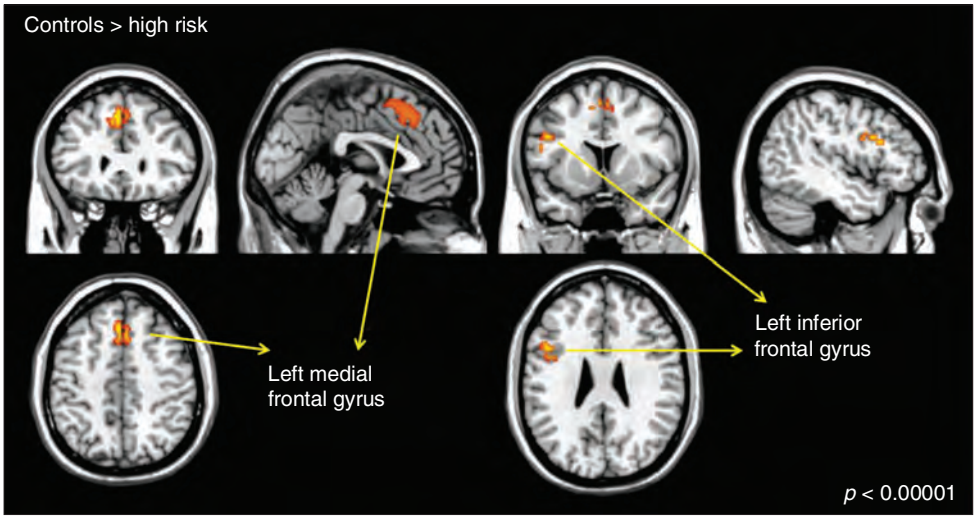

Fig. 1: Voxel-wise signed differential mapping meta-analysis of neurofunctional differences between patients at clinical high risk for psychosis and matched controls across different functional magnetic resonance imaging tasks. The left side of the brain is left on the figure.

inferior frontal response is associated with psychopathologic improvement of prodromal symptoms over time.[13] Medial frontal and superior frontal gyri are part of the dorsolateral prefrontal cortex, and fMRI alterations in these areas are thought to underlie executive and working memory dysfunctions in prodromal psychosis[10,44] (for a review of neurocognitive impairments in high-risk patients see Simon and colleagues[45]) and in established disease.[46] Similarly, the anterior cingulate has been associated with impairments in emotional processing and higher executive performances (for a review see Baiano and colleagues[47]). Previous fMRI studies have revealed abnormal anterior cingulate engagement in patients with first-episode psychosis,[48–50] patients at high genetic risk for psychosis[51,52] and in high-risk individuals.[10] A recent SDM voxel-based meta-analysis confirmed anterior cingulate (and insular) grey matter reductions in patients with first-episode psychosis, suggesting that the general salience network is abnormal from the early phases of disease.[53] Interestingly, longitudinal structural changes in the anterior cingulate of high-risk patients are associated with functional outcomes.[13] Anterior cingulate function and structure has also been reported to be especially sensitive to remedial antipsychotic treatment in patients with psychosis.[54,55] Because there is evidence indicating that a few weeks of antipsychotic treatment modulates the anterior cingulate response,[50,56] and because the latter has been associated with longitudinal functional outcomes in at-risk patients,[57] the question of the functional significance of dynamic cingulate changes in the prodromal phases of psychosis may have some potential clinical implications for preventive interventions.

The alterations described in the present study do not represent an effect of medication or illness duration[58,59] and can be interpreted as core neurofunctional abnormalities underlying an enhanced clinical vulnerability to psychosis. In a recent voxel-based meta-analysis of voxel-based morphometry (VBM) studies in high-risk patients, my group confirmed grey matter alterations in similar brain regions, including the anterior cingulate, the medial and middle frontal gyrus and the inferior frontal gyrus.[6] It is thus possible that structural and functional alterations share a common pathophysiology during prepsychotic phases. In line with this hypothesis, an fMRI–VBM study of high-risk patients confirmed that reduced prefrontal activation during working memory was associated with grey matter reductions in the same region.[57] Future multimodal imaging studies in such a population are expected to ascertain the strict correlation between structural and functional alteration during the prodromal phases of psychosis.

Table 2: Neurofunctional abnormalities underlying clinical vulnerability to psychosis

Comparison; brain region	Side	BA	Peak local maximum					
			Coordinate					
			x	*y*	*z*	SDM	*p* value	Ke
Controls > high-risk								
MFG	L	8	–4	26	44	0.323	< 0.001	292
MFG	L	8						59
Cingulus gyrus	L	32						31
SFG	L	8						52
SFG	R	8						41
MFG	R	8						22
SFG	L	6						43
SFG	R	6						29
IFG	L	9						76
IFG	L	9	–46	16	22	0.275	< 0.001	36
High-risk > controls	—	—						—

BA = Brodmann area; IFG = inferior frontal gyrus; Ke = cluster extent; L = left; MFG = medial frontal gyrus; R = right; SDM = signed differential mapping; SFG = superior frontal gyrus.

Limitations

Limitations of the current study are well acknowledged. The small sample size, although similar to those of previous voxel-based meta-analyses,[60] limited the power of the analyses, particularly subanalyses of groups at differential clinical risk for psychosis (i.e., APS v. BLIPS v. GRD), of different fMRI paradigms (i.e., cognitive v. affective) and of correlations with presenting symptoms. In addition, as suggested by some authors,[53] meta-analyses of voxel-based imaging studies are generally limited by the reported findings of individual studies, which do not allow for the estimation of effect sizes or the precise determination of the relative strengths of neurofunctional differences. To circumvent this problem, I recorded the statistical significance of the main findings and the method employed to correct the whole-brain results for multiple comparisons. An additional limitation concerns the methodologic differences of fMRI studies. These include differences in smoothing kernel size, slice thickness and statistical threshold. The most important caveat of imaging meta-analyses is the differential association with the various endophenotypes of the illness. The observed neurofunctional differences may reflect the composite psychopathologic status of the high-risk group, which includes true high-risk patients (in whom psychosis will later develop) and patients who are at high risk but will not become psychotic.[61] The cross-sectional design of the included studies prevented the clarification of their long-term clinical outcomes, and the extent to which the observed findings relate to the subsequent onset of psychosis remains to be determined.[62] Similarly, the dynamic interplay between neurofunctional markers of psychosis vulnerability and other environmental factors[63] is still mostly unknown. Although I attempted to address the effect of variables, such as sample size, age, sex and imaging parameters, other factors, such as substance abuse, cognitive functioning and personality traits, could potentially increase heterogeneity across studies.[15] Also, the complex interaction between functional alterations and underlying neurochemistry (mainly implicating DA and glutamate[14,64]) during the prepsychotic phases is still mostly unknown. Longitudinal fMRI studies involving patients at clinical risk for psychosis will be able to definitively ascertain the core neurofunctional alterations underlying the onset of psychosis.

Conclusion

Despite its limitations, the present meta-analysis indicated that patients at clinical high risk for psychosis show consistent

alterations in prefrontal activation across different task modalities. Such abnormalities may represent neurophysiologic correlates of an increased vulnerability to psychosis.

Competing interests: None declared.

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