Psychiatry Research: Neuroimaging 221 (2014) 69–77

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Multimodal voxel-based meta-analysis of structural and functional magnetic resonance imaging studies in those at elevated genetic risk of developing schizophrenia

Deborah Cooper [a,*], Victoria Barker [a], Joaquim Radua [b,c], Paolo Fusar-Poli [b], Stephen M. Lawrie [a]

[a] Division of Psychiatry, School of Clinical Sciences, Kennedy Tower, Royal Edinburgh Hospital, Morningside, Edinburgh, EH10 5HF, UK
[b] Institute of Psychiatry, King's College London, London, UK
[c] FIDMAG Research Unit, CIBERSAM, Sant Boi de Llobregat, Barcelona, Spain

ARTICLE INFO

Article history:
Received 10 October 2012
Received in revised form
3 July 2013
Accepted 25 July 2013
Available online 14 November 2013

Keywords:
Functional MRI
Genetic
Relatives
Voxel based morphometry
Multimodal
Schizophrenia

ABSTRACT

Computational brain-imaging studies of individuals at familial high risk for psychosis have provided interesting results, but interpreting these findings can be a challenge due to a number of factors. We searched the literature for studies reporting whole brain voxel-based morphometry (VBM) or functional magnetic resonance imaging (fMRI) findings in people at familial high risk for schizophrenia compared with a control group. A voxel-wise meta-analysis with the effect-size version of Signed Differential Mapping (ES-SDM) identified regional abnormalities of functional brain response. Similarly, an ES-SDM meta-analysis was conducted on VBM studies. A multi-modal imaging meta-analysis was used to highlight brain regions with both structural and functional abnormalities. Nineteen studies met the inclusion criteria, in which a total of 815 familial high-risk individuals were compared to 685 controls. Our fMRI results revealed a number of regions of altered activation. VBM findings demonstrated both increases and decreases in grey matter density of relatives in a variety of brain regions. The multimodal analysis revealed relatives had decreased grey matter with hyper-activation in the left inferior frontal gyrus/amygdala, and decreased grey matter with hypo-activation in the thalamus. We found several regions of altered activation or structure in familial high-risk individuals. Reliable fMRI findings in the right posterior superior temporal gyrus further confirm that alteration in this area is a potential marker of risk.

1. Introduction

Schizophrenia is a major psychiatric disorder throughout the world with an incidence of approximately 15 per 100,000 person years and a lifetime prevalence of 1% (Jablensky, 1997; Kirkbride et al., 2012). Schizophrenia is a highly heritable disorder with a multifactorial aetiology resulting from a combination of genetic factors and environmental interactions (Sullivan et al., 2003; Purcell et al., 2009; Johnstone et al., 2011). A number of genes have been suggested to confer specific increased risk, but interpreting this research remains complex due to the large number of candidate genes identified, the interaction between multiple genes of small effect and the variable clinical presentation of schizophrenia (Meyer-Lindenberg, 2010; Johnstone et al., 2011; Kim et al., 2011; Bondy, 2011). A complementary approach is to look at endophenotypes – the downstream consequences of risk genes (Bondy, 2011).

Both individuals with schizophrenia and their healthy relatives have been studied in an attempt to identify neuroanatomical markers of risk for psychosis. Relatives of those with schizophrenia do not meet the diagnostic criteria for illness, but do share common inherited genes (Rasetti and Weinberger, 2011). In addition, they partly share features such as socio-economic class, life experience and temperament (Rasetti and Weinberger, 2011). The advantage of using relatives is that external factors which may alter brain structure can be better controlled for. One such factor is increasing duration of illness, which has been associated with a thinner cortex in a number of brain regions in adults with schizophrenia (Van Haren et al., 2011). Antipsychotic drugs may also affect brain structure and function, with high-dose first generation antipsychotic use associated with more pronounced cortical thinning, as compared to second-generation antipsychotics (Van Haren et al., 2011).

Both individuals with schizophrenia and their relatives have demonstrated a number of subtle cognitive deficits (Park et al., 1995; MacDonald et al., 2003; Neelam et al., 2011; Fusar-Poli et al., 2012a; Karnik-Henry et al., 2012). Functional magnetic resonance

* Corresponding author. Tel.: +44 131 537 6000.
E-mail address: deborah.cooper@luht.scot.nhs.uk (D. Cooper).

0925-4927/$ - see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.pscychresns.2013.07.008

imaging (fMRI) uses deoxygenated haemoglobin as an endogenous tracer whilst individuals at genetic risk for schizophrenia perform cognitive tasks (Yurgelun-Todd et al., 1996). The neurochemical underpinnings of fMRI alterations in subjects at genetic risk for schizophrenia are unknown. However, a large systematic review of fMRI studies, in non-psychotic relatives of patients with schizophrenia, looked at alterations in brain perfusion in a number of cognitive tasks (Macdonald et al., 2009). This review found a number of areas of altered brain metabolism including the cerebellum, thalamus, basal ganglia, dorsal and ventral prefrontal, lateral temporal and parietal cortices (Macdonald et al., 2009). Unfortunately, the existing fMRI literature in the field is characterised by high heterogeneity and understanding this research or applying these findings remains complex due to a variety of factors including the use of a variety of cognitive tasks, different study populations and different imaging methods (Fusar-Poli et al., 2010). Unaffected siblings have also been shown to have a greater burden of subclinical symptoms. This includes symptoms such as social withdrawal and psychotic experiences (Velthorst and Meijer, 2012), as well as "proneness" to delusions (Schurhoff et al., 2003).

In voxel-based morphometry (VBM), structural MRI brain images are spatially normalised into the same stereotactic space, the grey matter segments smoothed and then statistical comparisons are made of grey matter images between healthy controls and subjects at genetic risk for schizophrenia (Ashburner and Friston, 2000). Already published meta-analyses of VBM studies in those at both genetic high risk and clinical high risk relatives found a number of grey matter volume reductions in the temporo-parietal, bilateral prefrontal and limbic cortices (Fusar-Poli et al., 2011a). Boos et al. have published a meta-analysis of hand-traced region-of-interest (ROI) structural imaging studies in genetic high-risk individuals and found reduced hippocampal volume, with a small reduction in total cerebral cortex volume and reduced volume of the third ventricle (Boos et al., 2007). A further recent meta-analysis comparing individuals at genetic high risk, those with a first-episode of psychosis and healthy control populations, has been carried out. This identified grey matter reductions in the left parahippocampal gyrus and bilateral anterior cingulate gyrus in individuals of familial high-risk status (Fusar-Poli et al., 2012c).

Despite increasing research in this area, it remains a challenge to clearly understand the functional and structural correlates of familial high-risk status. In part, this is compounded by the fact that many reports focus on individuals who are past the greatest risk period for the development of schizophrenia. Functional and structural correlates in those at familial high-risk may in fact represent compensatory changes, or markers of health, as opposed to risk. It could be assumed that areas showing functional alteration may also show structural changes. However, this is not clearly the case and may partly be due to the use of region-of-interest (ROI) techniques in fMRI and VBM studies, which can highlight focal differences that may not be readily replicable across studies. As such, there is a need for a better integration of the structural and functional findings across different modalities. To our best knowledge, this has never been attempted in subjects at heightened familial risk for schizophrenia.

The use of brain imaging studies in both individuals with schizophrenia and their relatives has much potential for identifying the neuroanatomical correlates of familial high risk for schizophrenia. The value of this approach is that we could isolate anatomical and/or functional disruptions in those brain regions which are most strongly associated with an elevated genetic risk for schizophrenia. These regions could therefore be foci of interest for further studies of relatives. Current research exploring the area of intervention in those at high risk for psychosis has primarily concentrated on those at clinical ultra-high risk. However, evidence for psychological intervention such as cognitive therapy, family therapy and pharmacological approaches continues to emerge, but remains inconclusive (Marshall and Rathbone, 2011; McGorry et al., 2013). Specific research in psychological approaches has suggested moderate evidence for cognitive behavioural therapy on reducing transition to psychosis at 12 months (Stafford et al., 2013) and reducing symptom burden (Morrison et al., 2012). Further, given the increasing interest in using neuroimaging to predict diagnosis and prognosis in those at genetic risk with psychosis, regions identified could also be predictive of the development of schizophrenia and perhaps even the identification of a prognostic or therapeutic sub-group.

The aim of this review was therefore to use a whole brain meta-analytical technique to examine regions which show alterations of either brain structure, function or both in individuals who are at familial high risk for schizophrenia by performing a multimodal meta-analysis of fMRI and VBM studies.

2. Methods

2.1. Search strategies

A literature search was performed on MEDLINE to identify potential fMRI and VBM studies including individuals at familial high risk for developing schizophrenia. The literature search was carried out between December 2011 and January 2012 and was performed by the first author (DC). The following search terms were used: "Schizophrenia", "relatives", "genetic high-risk", "fMRI" and "VBM". In addition, reference lists of identified articles were manually checked for potential studies not identified during the computerised search. The second author (VB) carried out a reliability check of the literature search. Fig. 1 details the process of the literature search and article inclusion according to the PRISMA guidelines.

2.2. Inclusion/exclusion criteria

To qualify for inclusion within the meta-analysis, the following criteria were used:

(1) Article should be an original paper in a peer-reviewed journal.
(2) Either whole brain fMRI or VBM imaging should have been performed.
(3) The article should include individuals at familial high risk for psychosis compared to a healthy control group.
(4) Individuals included in the study should be anti-psychotic naïve.
(5) Articles should detail either the Talairach or Montreal Neurologic Institute coordinates of altered brain regions.
(6) Brain coordinates should use a "whole brain" approach. Those using ROI or small volume correction (SVC) approaches were excluded.
(7) Language of publication was not a specific search criterion, but the included articles were in English.
(8) Articles exclusively examining those with a diagnosis of 22q11.2 deletion syndrome were not included.

Studies were then checked by two researchers to assess agreement with the above exclusion/inclusion criteria (DC & VB). Where multiple articles were identified that used the same cohort, the one with the largest sample size was selected. The 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) guidelines were used to achieve a high standard of reporting (Moher et al., 2009). Tables 1 and 2 detail the articles included within the study, and the baseline data extracted.

2.3. Recorded variables

Once the studies were selected, variables were extracted for inclusion in the meta-analyses. These included sample size, percentage of female participants, mean age of participants, imaging package, full width at half maximum (FWHM) of the smoothing kernel, task employed, magnet intensity and statistical method used. This information is included in Table 1 and Table 2. Statistically significant co-ordinates were extracted, including the direction of activation or volume difference change between control and high-risk individuals.

2.4. Meta-analyses

Structural brain abnormalities were voxelwise meta-analysed with the Effect-Size version of Signed Differential Mapping (ES-SDM) (Radua and Mataix-Cols,