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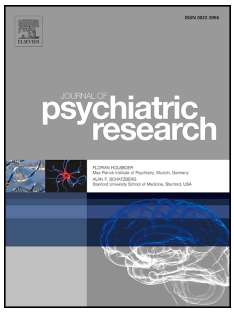

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Title Page

Exploring neural dysfunction in 'clinical high risk' for psychosis: A quantitative review of fMRI studies

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Abstract

Individuals at clinical high risk (CHR) of developing psychosis present with widespread functional abnormalities in the brain. Cognitive deficits, including working memory (WM) problems, as commonly elicited by n-back tasks, are observed in CHR individuals. However, functional MRI (fMRI) studies, comprising a heterogeneous cluster of general and social cognition paradigms, have not necessarily demonstrated consistent and conclusive results in this population. Hence, a comprehensive review of fMRI studies, spanning almost one decade, was carried out to observe for general trends with respect to brain regions and cognitive systems most likely to be dysfunctional in CHR individuals. 32 studies were included for this review, out of which 22 met the criteria for quantitative analysis using activation likelihood estimation (ALE). Task related contrast activations were firstly analysed by comparing CHR and healthy control participants in the total pooled sample, followed by a comparison of general cognitive function studies (excluding social cognition paradigms), and finally by only looking at n-back working memory task based studies. Findings from the ALE implicated four key dysfunctional and distinct neural regions in the CHR group, namely the right inferior parietal lobule (rIPL), the left medial frontal gyrus (lmFG), the left superior temporal gyrus (lSTG) and the right fronto-polar cortex (rFPC) of the superior frontal gyrus (SFG). Narrowing down to relatively few significant dysfunctional neural regions is a step forward in reducing the apparent ambiguity of overall findings, which would help to target specific neural regions and pathways of interest for future research in CHR populations.

Keywords

fMRI; clinical high risk; at-risk mental state; psychosis; review; meta-analysis

1. Objectives of the study and background

It is well known that psychosis like symptoms often emerge prior to the onset of full blown illness in late adolescence or early adulthood, followed by the classical clinical symptomatology (Lieberman et al, 2001; Yung et al., 1998). These early symptoms can be captured by various operationally defined criteria, such as the Personal Assessment and Crisis Evaluation (PACE) criteria, based on the presence of prodromal symptoms, including attenuated or brief intermittent psychotic symptoms, and/or significant recent deterioration in global functioning in the presence of high genetic risk (Yung and McGorry, 1996; Yung et al, 2006; Yung et al., 1998; Phillips et al, 2000). Together, these approaches have been proposed to form the clinical high risk criteria for both clinical and research studies (Pantelis et al 2003; Phillips et al, 2000; McGorry et al, 2000). Individuals at clinical high risk (CHR) for developing psychosis are also referred to as ultra-high risk (UHR) or simply as at-risk mental states (ARMS). A recent meta-analysis by Kaymaz and colleagues (2012) on long term longitudinal clinical data has shown that the yearly risk of conversion to psychosis is significantly higher in those with subthreshold psychotic symptoms (Yung et al, 2007).

It is believed that neuroimaging used in conjunction with clinical criteria may improve the understanding of transition states in the CHR population. The relative absence of potential confounders such as long term illness effects, substance and medication use, and age related neural changes, is an added advantage. The inclusion of neural biomarkers to the clinical syndrome might increase the overall predictive power of the CHR criteria, possibly enabling further prediction of clinical outcomes in the context of early intervention (Keshavan et al., 2010; Cannon et al., 2008; Ruhrmann et al., 2010). Neuroimaging researchers over the past decade have claimed that individuals at CHR have brain abnormalities that are similar to those with schizophrenia and first episode psychosis, with common structural abnormalities mainly found in prefrontal, medial temporal and anterior cingulate regions (Yucel et al 2003; Borgwardt et al 2007; Fornito et al 2008; Jung et al, 2010).

As with established psychotic disorders, a range of cognitive deficits, including working memory problems, are commonly found in the CHR phase (Pflueger et al, 2007), yet their neural substrates are not fully understood. The n-back task is one of the most commonly used paradigms for the investigation of the neural basis of working memory, requiring real time monitoring, updating and manipulation of remembered information (Gevins & Cutillo, 1993; Owen et al, 2005). It is believed that frontal and parietal regions play an important role in

working memory, with dorsolateral prefrontal cortex and ventrolateral prefrontal cortex being implicated most consistently (D'Esposito et al, 1998; Owen 2000). Similarly, other generalised executive and social cognition dysfunctions are also observed in the CHR phase.

In 2005, Morey and colleagues published the first fMRI study with an executive function paradigm on a CHR sample, and since then, the number of functional imaging studies in at-risk populations has grown steadily, but results seem to have been diverse and inconsistent. For almost a decade, a range of cognitive tasks have been employed tapping both general cognitive and social cognition paradigms with a view to identifying dysfunctional regions of the brain in people at risk for psychosis. Our aim was therefore to comprehensively and systematically review and synthesise the functional imaging evidence in the CHR subjects in the hope that some general trends would emerge with respect to brain regions and cognitive systems most likely to be dysfunctional in this population.

We carried out a literature review of functional MRI (fMRI) studies on CHR samples, firstly to find out if there were key dysfunctional neural regions, underlying the cognitive deficits in the at-risk phase in general. Secondly, we were particularly interested to explore whether general cognitive function, including working memory deficits, particularly those elicited through n-back tests, were related to one or more distinct neural regions or systems.

2. Materials and methods

2.1. Search strategy and inclusion/exclusion criteria

A search strategy using the following combination of words - "at-risk mental states, ARMS, clinical high risk, CHR, ultra-high risk, UHR, functional MRI, fMRI" was used to search for relevant literature on PubMed, Medline, Web of Science and PsycInfo databases. We used the term 'CHR' to include all 'at-risk' cases defined by internationally accepted clinical criteria, as stated subsequently. Studies between January 2001 and December 2013 were searched, although peer reviewed publications in English were only considered for the review. The essential inclusion criteria comprised studies, which (i) defined CHR by established clinical instruments/criteria; (ii) had either cross sectional or longitudinal designs; (iii) had a healthy control (HC) group for comparison; (iv) and, which acquired BOLD data (the added presence of structural MRI results and/or multimodal imaging findings were also acceptable) on either 1.5T or 3T systems. Established clinical instruments were limited to the Comprehensive Assessment of At Risk Mental States (CAARMS), which also includes

genetic/familial risk for psychosis coupled with decline in functioning in addition to attenuated positive symptoms and brief limited intermittent psychotic symptoms (Yung and McGorry, 1996); the Structured Interview for Prodromal Symptoms (SIPS) which includes positive, negative, disorganisation and general symptoms, and Scale of Prodromal Symptoms (SOPS), which are modelled on the CAARMS criteria (Miller et al, 2003); and Bonn Scale for the Assessment of Basic Symptoms (BSABS), which incorporates operational symptom definitions in order to identify individuals at an earlier stage of psychosis prodrome (Klosterkotter et al, 2001). Although the vast majority of MR brain studies were expected to have been carried out on 1.5T scanners, no restrictions were specifically imposed on higher scanner strength to enable the inclusion of more recent studies. As functional imaging studies on clinical high risk populations were expected to have been carried out by relatively few academic centres since Morey and colleagues' (2005) first study with 10 CHR and 16HC, a minimum sample size, comprising at least 20 participants was considered to be appropriate for the quantitative review, which was also similar to acceptable standards for fMRI studies (Murphy and Garavan, 2004). No further restrictions on the samples were imposed such as history of past substance misuse and/or the intake of prescribed psychotropics, in order to present a pragmatic and real world view of the high risk cohort, clinical course and acceptable therapeutic interventions in this critical period. Studies were specifically excluded from the review if (i) clinical high risk groups were categorised solely on the basis of familial (first and/or second degree) genetic high risk; (ii) organic brain lesions/neurological illnesses were present in the participants; (iii) there was an absence of a comparative healthy control group; (iv) and presence of imaging methods other than fMRI, such as structural and/or PET/SPECT methods, were solely employed for data acquisition. Extraction of data from studies was performed independently by 4 researchers (AD, HT, LF, LS) to ensure no researcher bias would persist before concatenating all extracted data for analysis. All data extracted for the purpose of this review are listed in Tables 1 and 2.

2.2 Qualitative and quantitative analysis of pooled fMRI data

Following selection of eligible studies, fMRI data were pooled and further sorted into those that contrast CHR with at least HC, containing functional activation coordinates (Talairach or MNI), and those without between-group effects and/or lacking adequate quantitative data on activation coordinates. The latter studies were nevertheless included for a qualitative summary, whereas the former group were included for quantitative estimation using Activation Likelihood Estimation (ALE) a meta-analysis method developed by Turkeltaub et

al (2002) and adopted by BrainMap (Laird et al., 2005). 'Ginger ALE' was used to compute the results (Eickhoff et al, 2009).

Task related contrast activations were analysed with ALE separately, as (i) decreased activations in the CHR and (ii) increased activations in CHR, in comparison to HC in the total pooled sample. Whether any differences in activation patterns between CHR and HC would emerge, if studies with social cognition paradigms were specifically excluded from the rest of the pooled sample, comprising all the generalised cognitive function type studies, including n-back designs, were further explored. Lastly, we examined whether activation patterns in a subset of studies, which solely employed the n-back task, would differ from the larger pooled sample. ALE was based on MNI spatial normalisation template, and wherever necessary, Talairach coordinates were transformed into MNI space before pooling data for analysis. Threshold levels for the ALE were observed at $p<0.01$ with a spatial cluster threshold $>200mm^3$ to understand the pattern of brain activation in the CHR population. A false discovery rate (FDR) corrected threshold of $p<0.05$ is not unusual for a meta-analysis of fMRI tasks in clinical populations such as schizophrenia (Goghari, 2011). Nevertheless, we set a more stringent threshold level of $p<0.01$ (FDR) with cluster threshold $>200mm^3$ to further minimise type I errors. High activation ALE clusters based on the x, y and z axes of the weighted centre of mass and peak locations in MNI space were produced along with cluster volumes. Image reconstruction of ALE was further carried out using standardised T1 weighted templates on Multi Image Analysis GUI (MANGO), developed by the University of Texas Health Science Center.

2.3 Categorisation of cognitive paradigms

Neurocognitive deficits observed in psychosis can be broadly grouped into two categories, namely generalised cognitive functioning and social cognition. Generalised cognitive functioning includes specific domains such as memory functioning, global cognitive functioning, language, executive functioning and attention, and impairment of these functions in schizophrenia have been substantiated by meta-analytical reviews (Reichenberg, 2010; Fioravanti et al, 2012). The understanding of social cognition in schizophrenia focuses primarily on the areas of theory of mind, social perception, social knowledge, attributional bias and emotional processing with overlapping boundaries between these categories, as proposed by an NIMH consensual workshop (Green et al, 2008). Evidence strongly suggests that deficits in both these categories of cognitive functioning are present at the prodromal and

first episode psychosis stage of the illness (Aas et al, 2014). Social cognition networks tend to overlap with the default mode network, and are also likely to be distinct from those associated with more generalised cognitive functions (Mars et al, 2012; Billeke and Aboitiz, 2013), hence further sub-grouping of cognitive paradigms, following initial pooling of all data for the quantitative analysis, on the basis of these two broad categories of cognitive deficits were carried out.

3. Results

3.1. Studies pooled

142 separate studies were initially pooled with the key words in literature search, out of which 32 studies between 2005 and 2013, meeting the inclusion criteria, were considered for this review (Figure 1). Out of these, 22 studies (Seiferth et al, 2008; Broome et al, 2009; Fusar Poli et al, 2009; Allen et al, 2010; Broome et al, 2010a; Fusar-Poli et al, 2010a, 2010b; Pauly et al, 2010; Sabb et al, 2010; Allen et al, 2011a, 2011b; Brune et al, 2011; Fusar-Poli et al, 2011a, 2011b, 2011c; Smieskova et al, 2011; Valli et al, 2011; Allen et al 2012; Choi et al, 2012; Gee et al, 2012; Karlsgodt et al, 2013; Niendam et al, 2013) were further observed to be suitable for quantitative analysis with ALE (Table 1). A qualitative representation of collective activation foci based on different cognitive paradigms across the studies has been provided in Figure 2. The remaining studies (Morey et al, 2005; Benetti et al, 2009; Crossley et al, 2009; Broome et al, 2010b; Shim et al, 2010; Jung et al, 2012; Dandash et al, 2013; Fryer et al, 2013; Pettersson Yeo et al, 2013; Schmidt et al, 2013) although relevant for the review in general, were excluded from the ALE analysis, as there were either insufficient data on contrast coordinates or a lack of significant main group differences (Table 2).

It was also noted that there was considerable overlap of participants used in different studies, but with different cognitive paradigms, particularly from the same academic centres. Because of this, narrowing down the studies of interest by first examining those which probed cognitive functions (including and excluding studies tapping social cognition), and then more specifically only those using the n-back paradigm to minimise potential repetition of overlapping participants, was also statistically relevant.

3.2. Activation likelihood estimation of functional MR data

3.2.1. Decreased activation patterns

3.2.1a. Total sample irrespective of nature of cognitive paradigms (Broome et al, 2009; Fusar Poli et al, 2009; Fusar Poli et al, 2010a; Fusar Poli et al, 2010b; Pauly et al, 2010; Allen et al, 2011a; Allen et al, 2011b; Brune et al, 2011; Choi et al, 2011; Fusar Poli et al, 2011b; Gee et al, 2011; Valli et al, 2011; Allen et al, 2012; Smieskova et al, 2012; Niendam et al, 2013) - Quantitative analysis with ALE of the pooled sample showed decreased activations in the right inferior parietal lobule and left medial frontal gyrus in CHR in comparison to HC at $p<0.01$ (Table 3)(Figure 3).

3.2.1b. Pooled sample excluding social cognition paradigms

CHR subjects continued to show reduced activation in the right inferior parietal lobule and left medial frontal gyrus at $p<0.01$ even when studies using social cognition paradigms (Seiferth et al, 2008; Brune et al, 2011; Gee et al, 2012) were excluded (Table 3).

3.2.1c. Studies employing n-back paradigm only (Broome et al, 2009; Fusar Poli et al, 2010a; Fusar Poli et al, 2011b; Smieskova et al, 2012) - Only the right inferior parietal lobule still showed decreased activation in the CHR when compared to HC at $p<0.01$ (Table 3).

3.2.2. Increased activation patterns

3.2.2a. Total sample irrespective of nature of cognitive paradigms (Seiferth et al, 2008; Broome et al, 2009; Fusar Poli et al, 2009; Allen et al, 2010; Pauly et al, 2010; Brune et al, 2011; Choi et al, 2011; Fusar Poli et al, 2011a; Fusar Poli et al, 2011c; Allen et al, 2012; Karlsgodt et al, 2013) - There was evidence of increased activations in the CHR compared to HC in the left superior temporal gyrus and right superior frontal gyurs at $p<0.01$ (Table 3) (Figure 4).

3.2.2b. Studies excluding social cognitive paradigms

Increased regional activation only in the right superior frontal gyrus, particularly the frontopolar cortex, was still observed in CHR in comparison to HC at $p<0.01$, when studies utilising social cognition paradigms (Seiferth et al, 2008; Brune et al, 2011) were excluded from the pooled sub-sample (Table 3).

3.2.2c. Studies employing n-back paradigm only

Studies employing the n-back cognitive tasks did not show any evidence of increased activations in any brain region in the CHR group at $p<0.01$ (Table 3).

4. Discussion

The collated qualitative findings provide evidence of widespread functional deficits in clincal high risk groups, covering almost all major regions of the brain, including the prefrontal and medial frontal regions, the parietal and temporal lobes, the occipital cortices and even the cerebellum. There would appear to be involvement of widespread overlapping of brain regions and pathways, which could be interpretted to suggest a generalised neural vulnerabiliy and network dysfunction, underlying the cognitive deficits in CHR. However, findings from the ALE implicated four key dysfunctional cortical regions with a high degree of certainty, namely the right inferior parietal lobule (rIPL), the left medial frontal gyrus (lmFG), the left superior temporal gyrus (lSTG) and the frontopolar cortex (FPC) in the right superior frontal gyrus (rSFG).

4.1. Decreased rIPL and lmFG activation in CHR

We observed reduced activation of the rIPL and lmFG in the CHR group when compared to HC in the total sample. Only the rIPL hypoactivation remained evident when the n-back studies were specifically pooled together. However, the cluster volumes differed across the three subgroups. As expected, there was a positive relationship with the number of cognitive tasks employed and cluster volumes, with n-back only studies showing a considerably smaller volume of hypoactivation in contrast to the larger sub-sample (all generalised cognitive paradigms) and total pooled sample (including social cognition paradigms). Most of the functional imaging studies pooled for the ALE primarily focussed on working memory and verbal fluency and/or other executive function paradigms (Table 1), although few studies did employ emotional faces (Seiferth et al, 2008; Gee et al, 2012), theory of mind (Brune et al, 2011) and even random movement generation (Broome et al, 2010a) tasks. It appears that the rIPL is more specific for working memory tasks, whilst generalised executive functions tend to additionally involve the frontal lobe. Working memory involves several different functional components, which are regulated by multiple brain regions, and abnormalities in both the verbal and spatial domains are commonly observed in psychotic disorders (Barch, 2005). The IPL and intraparietal sulcus have been consistently implicated in working

memory research, and the fronto-parietal network in particular is involved in cognitive control, regulating working memory updates, attentional selection, error monitoring and declarative memory retrievals (Wager and Smith, 2003; Anderson et al, 2004, 2008; Borst and Anderson, 2012). The importance of the IPL in the pathophysiology of schizophrenia, although often overlooked in literature, has been highlihted by Torrey (2007). The IPL, being an essential component of the heteromodal association area, integrates information from visual, auditory and sensory modalities, and is also involved in the evaluation of information and planning of response (Pearlson et al, 1996) which may be relevant to schizophrenia (Torrey, 2007). Therefore, it seems that, in CHR individuals, regardless of performance, n-back working memory tasks produce less activation on fMRI in relevant specific brain regions, in comparison to the larger group of executive function paradigms with frontal lobe involvement, as expected.

A recent meta-analysis by Radua et al (2012) also found evidence of decreased grey matter volume and functional abnormalities in the medial frontal/anterior cingulate cortex and insula/superior temporal gyrus bilaterally in first episode psychosis patients. Reduced activation of the medial frontal gyrus bilaterally and reduced gray matter volume in the left medial frontal gyrus, amongst other regions, has also been observed in previous meta-analyses on clinical high risk subjects (Fusar-Poli et al, 2011; Fusar-Poli, 2012). Taylor et al (2012) has also provided meta-analytical evidence of reduced medial frontal activation in schizophrenia, in addition to several other brain areas. Our finding of lmFG hypoactivation in CHR during generalised cognitive function tasks appeared to be consistent with these previous observations. This remain unchanged whether social cognition paradigms were included or not in the pooled sample. However, the volume of hypoactivation reduced further in this area in the absence of social cogntion tasks.

4.2. Increased lSTG and rSFG activation in CHR

The meta-analysis found a reliable increase in activation in the lSTG and FPC in the rSFG in CHR when compared to HC. The STG has been a frequent and consistent region of interest in schizophrenia research, showing both structural and functional abnormalities associated with psychosis symptomatology, such as auditory hallucinations (McGuire et al, 1995; Fletcher et al, 1996; Wright et al, 2000; Honea et al, 2005; Kuroki et al, 2006; Allen et al, 2007; Homan et al, 2013). fMRI meta-analysis in schizophrenia has also demonstrated hyperactivation of

the superior temporal gyrus, amongst other regions (Taylor et al, 2012). Homan and colleagues (2013) demonstrated increased regional cerebral blood flow (CBF) in the lSTG in patients with schizophrenia (pre and post treatment with transcranial magnetic stimulation) in comparison to control participants. Meta-analysis of diffusion tensor studies have demonstrated reductions of fractional anisotropy of grey and white matter in the STG, which is smaller on the left side (Wright et al, 2000; Shenton et al, 2001; Antonova et al, 2005; Ellison-Wright & Bullmore, 2009). Takahashi and colleagues (2010) found that those at risk of psychosis had reduced grey matter in the STG before the onset of the illness. ALE meta-analysis of emotional perception tasks in schizophrenia has also demonstrated greater activation in the STG amongst other structures (Taylor et al, 2012), which appeared to be similar to our findings, as we also did not find further evidence of lSTG hyperactivation in the CHR sample, once social cognition paradigms were excluded from the pooled sample. Furthermore, n-back working memory tasks in particular seemed to have no effect on STG activation.

Hyperactivation of the FPC in the rSFG in the CHR group was also observed with generalised cognitive functions. The right FPC is specifically implicated in visual-spatial prospective memory (Costa et al, 2013). Frontopolar hyperactivation has also been observed in schizophrenia when compared to controls with working memory tasks (Sugranyes et al, 2012). A recent near-infrared spectroscopy (NIRS) study has also demonstrated evidence of abnormality of this region, which was specific for individuals with schizophrenia in comparison to those with major depressive disorder (Kinou et al, 2013). The anterior prefrontal cortex, including frontopolar Brodmann area 10, underlies the human ability to monitor and reflect on cognition and experience, including the capacity to introspect in the areas of perception and memory (Baird et al, 2013), and problems in these domains are likely to be present in the CHR phase.

4.3. Pattern of activation and choice of cognitive paradigms

It seemed likely that the choice of cognitive paradigms influenced specific neural regions, associated with those tasks. Figure 2 demonstrates how both generalised executive function and social cognition paradigms across the different studies activate multiple and overlapping regions, convering the whole brain, although frontal regions appear to be most commonly implicated in most studies. Studies commonly employed tests of working memory (Broome et al, 2009; Fusar Poli et al, 2010a; Fusar Poli et al, 2010b; Pauly et al, 2010; Allen et al,

2011a; Allen et al, 2011b; Fusar Poli et al, 2011b; Smieskova et al, 2011; Choi et al, 2012; Karlsgodt et al, 2013; Niendam et al, 2013), followed by other generalised cognitive functions, including verbal fluency and language processing tasks (Fusar Poli et al, 2009; Allen et al, 2010; Sabb et al, 2010; Fusar Poli et al, 2011a; Fusar Poli et al, 2011c; Valli et al, 2011; Allen et al, 2012). We did not find a sufficient number of studies with exclusively social cognition paradigms, including theory of mind and emotional tasks, to group and analyse separately for decreased and increased activations (Seiferth et al, 2008; Brune et al, 2011; Gee et al, 2012), although their exclusion from the pooled sample provided interesting insights. Social cognition includes theory of mind, emotion and empathy, and deficits in these domains are often found in schizophrenia, and appear to be independent of generalised cognitive deficits (Frith, 1992; Frith and Corcoran, 1996; Lee et al, 2004). The inclusion of social cognition paradigms seemed to influence the additional hyperactivation cluster (lSTG), as observed in the ALE findings. Pathways for social cognition comprise the temporal cortex and the amygdala, interacting with the prefrontal cortex, and although theory of mind and empathy networks possibly overlap, the former is believed to be more strongly mediated by temporal lobe structures and fronto-temporal networks (Lee et al, 2004). Thus, it may not be so surprising that when fMRIs employing social cognitive paradigms were included in the pooled sample, the quantitative results pointed more towards temporal lobe dysfunction, with possibly fronto-temporal pathway abnormalities, which was in contrast to specific working memory type paradigms, possibly involving different neural regions and pathways, such as the parietal lobe and fronto-parietal networks (Berryhill and Olson, 2008; Borst and Anderson, 2012). Owen and colleagues (2005) in their meta-analysis found evidence for consistent activation of six key frontal and parietal cortical regions by three variants of the n-back paradigm, namely the dorsolateral prefrontal, ventrolateral prefrontal, rostral prefrontal, bilateral and medial premotor, and the bilateral and medial posterior parietal cortices. Structural and functional dysconnectivity is believed to be a central underlying feature of schizophrenia, and several studies have found evidence of disruption in the fronto-temporal and fronto-parietal networks (Mesulam, 1998; Davis et al, 2003; Shergill et al, 2007), hence, it would not be surprising to find similar network dysfunctions in the CHR phase of the disorder, which would merit further investigations in the future.

In our study, we found that the n-back task was exclusively associated with hypoactivation of the rIPL in the CHR group, unlike other functional paradigms which showed evidence of both increased and decreased regional activations. Hyper and hypo-activations between

groups need to be interpreted carefully, which should also take into account differences in performance. Some early studies suggested better task performance to be correlated with relative increase in brain activity whereas others correlated better performance with reduced brain activation (Haier et al, 1992; Ragland et al, 1997, Jansma et al, 2001). It is believed that activation patterns do not necessarily demonstrate a straight forward linear relationship but a capacity-constrained response with task performance in the form of an inverted U-shape, most likely influenced by the working memory capacity of the subject (Callicott et al, 2003). Hence, it may not be so surprising to find both increased as well as decreased activation patterns in those at risk of developing psychosis, depending on cognitive paradigms used, although the precise nature of such differential activation patterns and their inter-relation to one another across the whole brain is yet to be fully understood and also beyond the scope of this study at the present time.

4.4. Other fMRI studies not included in the ALE review

Other functional imaging studies which did not show significant group differences and/or adequate quantitative activation data (Table 2), also employed a range of executive function paradigms (Morey et al, 2005; Benetti et al 2009; Crossley et al, 2009; Broome et al, 2010b; Petterson-Yeo et al, 2013), and resting state acquisitions (Shim et al, 2010; Jung et al, 2012; Fryer et al, 2013). These studies, four of which were primarily based on a predetermined ROI approach (Morey et al, 2005; Jung et al, 2012; Fryer et al, 2013; Schmidt et al, 2013), highlighted several key brain regions, similar to those observed in the studies included in the ALE (Table 3), although dysfunctional areas were predominantly frontal and temporal. Morey and colleagues (2005) showed evidence of differential activation in the anterior cingulate, inferior frontal gyrus, and middle frontal gyrus on visual oddbal tasks in comparison to control groups, suggesting a decline in prefrontal functioning before the onset of illnes. Three studies with additional early onset psychosis participants, focused primarily on functional connectivity, and demonstrated a reduction of effective connectivity from the right posterior hippocampus to the right inferior frontal gyrus, possibly indicating increased vulnerability in those at high risk of developing psychosis (Benetti et al., 2009); an alteration of fronto-temporal coupling in early onset psychosis, although the results seemed to be less clear in those deemed as high risk of developing the disorder (Crossley et al, 2009); and progressive reduction in working memory induced modulation of functional connectivity from the middle frontal gyrus to the superior parietal lobule in the right hemisphere in CHR and first onset psychosis patients in comparison to healthy controls (Schmidt et al, 2013).

Data for carrying out dynamic causal modelling in the latter study was obtained from Smieskova et al (2011), the findings of which were included in the quantitative analysis (Table 1). These studies were based on working memory tasks with distinct paradigms, but failed to provide evidence for differences in localised regional activation between high risk and control subjects. Pettersson-Yeo and colleagues (2013), carried out a multimodal study, combining structural and fMRI along with DTI, genetic and cognitive data to differentiate between CHR, first episode psychosis and healthy controls, although there was an absence of main between- group fMRI differences between the CHR and HC groups. Resting state fMRI studies also demonstrated evidence for hyperconnectivity within the default mode network (DMN), and negative correlations between the posterior cingulate cortex and task related areas, suggesting alterations of intrinsic networks (Shim et al., 2010); and deficient higher load working memory DMN suppression in the CHR group (Fryer et al, 2013). Jung and colleagues (2012) in their multi-modal study, employing both structural and functional MRI scans with both resting state and executive function paradigms, demonstrated the likelihood of functional disconnections in Broca's area in both CHR and schizophrenia patients. Similar to the studies in the quantitative analysis, these also highlight the incosistent pattern of findings and complexity of functional network abnormalitites that underlie the clinical high risk phase.

4.5. Limitations of the quantitative analysis

The relative heterogeneity of cognitive paradigms in the pooled sample for quantiative analysis is a significant limitation in the context of robust interpretation and generalisation of findings. Undoubtedly, complex neuropsychological tasks involve a number of component processes, and it is somewhat artifical to class these as 'executive' or even 'working memory'. Nevertheless our grouping of task followed convention and enabled us to make broad inferences about functions and underlying brain systems, but these should be treated cautiously.

It seems that the complexity of functional deficits in high risk clinical groups mirrors those of early onset and established psychosis, which have also produced inconsistent results so far. Not all studies reported in this review were longitudinal in design, hence it was not possible to link apparently dysfunctional neurofunctional areas with transition to psychotic states. Another limitation is that many of the fMRI studies in CHR populations have been carried

out by a few neuroimaging groups, resulting in considerable overlap of participants in the pooled sample (Allen; Broome; Fusar-Poli and colleagues; 2009 - 2012). Three studies with Fusar Poli as first author (2009; 2010b and 2011b) had the same subjects, although three different fMRI paradigms (verbal fluency; paired associate learning test; n-back test) were used to acquire BOLD data. Similarly, two different fMRI paradigms (n-back task, verbal fluency) were employed on another group of similar subjects (Fusar-Poli 2010a; 2011a). Broome and colleagues (2009 and 2010a) also used two different experimental paradigms (n-back and random movement generation) on 17 CHR and 15 healthy controls. Allen and colleagues (2010, 2011a, 2011b and 2012) did not have identical participants in the four studies, although they acknowledged that the 2012 study included the participants in the study carried out by Broome et al (2009) . These could potentially bias the analysis since the data were obtained from a restricted pool and the observations cannot be considered independent, thereby restricting generalisability. However, the use of different experiments within the same subjects make the studies distinct, in terms of variability in acquisition, design and analytical approaches, and in principle, should cause a reduction in error variance associated with individual differences (Barlow and Hayes, 1979). However, for statistical robustness, a reconfirmatory analysis, excluding only the relatively small and potentially overlapping samples from the London area (Broome; Fusar-Poli and colleagues; 2009 – 2012; Allen et al 2010, 2011b; Valli et al, 2011) and regardless of fMRI paradigms and associated cognitive demands in the pooled sample, still demonstrated the activations of the rIPL and lSTG. The absence of the two remaining activation coordinates was obvious, as a result of loss of other fMRI paradigms, and these observations do not contradict the original findings. The fact that the results remain similar in spite of limiting the amount of potentially overlapping studies, further strengthens our findings. Although other studies using ALE have usually adopted a less stringent approach with minimum cluster thresholds at $100mm^3$ and $p<0.01$ (FDR), we deliberately set higher thresholds to reduce the possibility of Type 1 errors. The pooled analysis of n-back studies helped to mitigate the problem of subject overlap, and also reduced another source of heterogeneity due to the differing cognitive paradims employed. Finally, a weakness of the methodology used including ALE is that it relies on the selection of 'significant' results by contributing authors, rather than, as in other meta-analyses in biomedicine, making use of effect sizes of differences between interventions of interest which can be pooled to see if indeed, they show an overall statistically significant effect. Not only does this selection restrict the number of contrasts, it biases the regions of potential interest that can be examined to those favoured by the researchers and magnifies

publication bias. Furthermore, the methodology and findings of this study were wholly limited to a quantitative assessment of BOLD response, and did not allow for a more integrated assessment of brain function alongside behavioural performance in the selected pool, which was beyond the scope of the current approach. It would have ideally provided a far greater understanding of the activation coordinates in both at-risk and control subjects, and should be addressed in future research.

Very few studies so far have collated quantitative fMRI data in CHR populations. As mentioned, Fusar-Poli (2012) in his voxel-wise meta-analysis of 9 specific functional MR studies (all included in the current ALE) found that high risk individuals had reduced neural activation in the left inferior frontal gyrus along with a cluster spanning the bilateral medial frontal gyrus and the left anterior cingulate. The study however did not find any evidence of increased neural activation in high risk individuals in comparison to healthy controls. Smieskova and colleagues (2013) have carried out a review of multi-modal brain imaging findings in both genetic high risk and clinical high risk samples, and concluded that neurofunctional deficits were mainly located in the prefrontal, medial temporal, subcortical, parietal and cerebellar regions. A most recent multimodal meta-analysis of structural and fMRI studies in genetic high risk population has demonstrated hyperactivation in the left inferior frontal gyrus/amygdala with decreased grey matter and thalamic hypoactivation with decreased grey matter in relatives of individuals with schizophrenia (Cooper et al, 2014).

Conclusion

Although cognitive deficits are believed to be central to the pathophysiology of schizophrenia (Barch, 2005), it is unclear whether dysfunction is evident in core brain regions, pathways or systems prior to the devlopment of the disorder, or that underlies a subset of the features of the full-blown clinical syndrome. Narrowing down to relative few and distinct consistently dysfunctional regions of the brain, especially in very early stages of the disease process, is a step forward in reducing the ambiguity and inconsistency of findings in at-risk literature. Generalised cognitive function tasksl appear to cause abnormal activation patterns in CHR individuals in the frontal regions bilaterally, and the right inferior parietal lobule, which also seems to be relatively specific for n-back working memory tasks; whereas social cognition functions seem to implicate the left temporal region in addition. The results from this study, along with supporting evidence from previous neuroimaging studies on psychosis specifically

implicate the rIPL, the lmFG, the lSTG and rFPC in the SFG as key dysfunctional regions, possibly subserving the fronto-parietal and the fronto-temporal networks, in individuals at high risk of developing the disorder.

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Table 1: CHR studies included for fMRI quantitative ALE analysis

Study (Location)	Sample						CHR Clinical Instrument/ Criteria	Imaging Details			Functional brain regions implicated in CHR (in comparison to controls)
	CHR (M,F)	Age	Other	Age	HC (M,F)	Age		fMRI paradigm	MR Scanner	Spatial normalisation template	
Seiferth et al, 2008 (Aachen, Germany)	12 (10M, 2F)	24.5	-	-	12 (10M, 2F)	24.5	SIPS	Facial Emotions for Brain Activation (Emotion discrimination)	1.5T Siemens Sonata	MNI	R lingual and fusiform gyrus, L middle occipital gyrus, inferior and superior frontal gyri, cuneus, thalamus, hippocampus
Broome et al, 2009 (London, UK)	17 (12M, 5F)	24.2	10^^^ (7M, 3F)	25.5	15 (11M, 4F)	25.4	CAARMS	N Back (Working memory)	1.5T Signa GE	Talairach	L & R inferior parietal lobule, L precuneus, R angular gyrus, R insula, L inferior frontal gyrus, R medial/superior frontal gyrus
Fusar Poli et al, 2009 (London, UK)	15 (8M, 7F)	24.36	-	-	15 (9M, 6F)	25.18	CAARMS	Verbal fluency task (Executive function)	1.5T Signa GE	MNI	Bilateral anterior cingulate, left inferior frontal gyrus
Allen et al, 2010 (London, UK)	15 (9M, 6F)	26.85	-	-	15 (8M, 7F)	25.75	CAARMS	Hayling Sentence Completion Task (Executive function)	1.5T Signa GE	MNI	R caudate and anterior cingulate cortex bilaterally
Broome et al, 2010a (London, UK)	17	24.2	10^^^	25.5	15	25.4	CAARMS	Random movement generation task	1.5T Signa GE	Talairach	Left insula, left post-central gyrus and left inferior parietal lobule
Fusar Poli et al, 2010a* (London, UK)	20	26.6	-	-	14	25.5	CAARMS	N-back task (Working memory)	1.5T Signa GE	MNI	Right middle frontal gyrus, medial frontal gyri, left superior parietal lobule
Fusar Poli et al, 2010b (London, UK)**	15 (8M, 7F)	24.36	-	-	15 (9M, 6F)	25.18	CAARMS	Paired associate learning test (Spatial working memory)	1.5T Signa GE	MNI	Left precuneus, left superior parietal lobule, right middle temporal gyrus
Pauly et al, 2010 (Aachen, Germany)	12 (10M, 2F)	24.22	-	-	12 (10M, 2F)	24.46	SIPS	N back task and olfactory stimulation (Working memory and emotion)	1.5T Siemens Sonata	MNI	Right superior temporal gyrus, thalamus, cerebellar regions
Sabb et al, 2010 (Los Angeles, USA)	25[3] 15[4]	16.8[3] 18.4[4]	-	-	24	18.5	SIPS	Topic maintenance vs Reasoning Task (Language processing)	3T Siemens Allegra	MNI	L inferior frontal gyrus, medial prefrontal regions, anterior cingulate, L middle and inf. temporal gyri, bilateral caudate, lingual gyrus, occipital cortex
Allen et al, 2011a (London, UK)	18 (10M, 8F)	27.10	-	-	22 (14M, 8F)	27.55	CAARMS	DRM false memory task (Working memory maintenance and manipulation)	1.5T Signa GE	MNI	L middle frontal gyrus, bilateral medial frontal gyri, L parahippocampal gyrus, med. temporal and prefrontal regions
Allen et al, 2011b (London, UK)*	20^ (10M, 10F)	26.3	-	-	14 (9M, 5F)	25.69	CAARMS	DRM false memory task (Working memory maintenance and manipulation)	1.5T Signa GE	MNI	Medial temporal lobe

Brune et al, 2011 (Bochum, Germany)	10 (7M, 3F)	25.5	22^^	26.8	26 (16M, 9F)	28.8	BSABS, SOPS	Computerised ToM Test (Theory of Mind)	1.5T Magnetom Symphony Siemens	MNI	Prefrontal cortex, posterior cingulate, temporoparietal cortex, medial frontal gyrus, left inferior frontal gyrus, TPJ, L sup. and middle temporal gyrus
Fusar Poli et al, 2011a (London, UK)*	20 (11M, 9F)	26.65	-	-	14 (10M, 4F)	25.54	CAARMS	Verbal fluency task (Executive function)	1.5T Signa GE	MNI	L inf. frontal & R middle frontal gyrus
Fusar Poli et al 2011b (London, UK)**	15 (8M, 7F)	24.36	-	-	15 (9M, 6F)	25.18	CAARMS	N-back task (Working memory)	1.5T Signa GE	MNI	Left middle frontal gyrus, supramarginal gyrus, inferior parietal lobule, anterior cingulate and right parahippocampal gyrus
Fusar-Poli et al, 2011c* (London, UK)**	24 (23M,1F)	26.6	-	-	17 (10M, 7F)	25.5	CAARMS	Verbal Fluency Task (Executive function)	1.5T Signa GE	MNI	Middle frontal gyrus bilaterally
Smieskova et al, 2011 (Basel, Switzerland)	17[1] (13M, 4F) 16[2] (11M, 5F)	25.24[1] 25.06[2]	21^^^	28.57	20 (10M,10F)	26.5	PACE criteria	N Back task (Working memory)	3T Siemens Magnetom Verio	MNI	Parietal and middle frontal regions
Valli et al 2011* (London, UK)**	22 (12M, 10F)	25.72	-	-	14 (6M, 8F)	25.62	CAARMS	DRM false memory task (Verbal episodic memory)	1.5T Signa GE	MNI	Left parahippocampal gyrus
Allen et al, 2012^^^^ (London, UK)*	41[+] (27M, 14F)	24.24	-	-	24[+] (16M, 8F)	25.46	CAARMS	Verbal Fluency Task (Executive function)	1.5T Signa GE	MNI	Bilateral prefrontal cortex, brainstem, left hippocampus
Choi et al, 2012 (Seol, South Korea)	21 (12M, 9F)	21.62	17# 15^^	20.71 # 23.47	16 (9M, 7F)	21.37	CAARMS	Spatial Delayed Response Task (Working memory)	1.5T Siemens AVANTO	MNI	Right IPL, DLPFC, left inferior temporal gyrus, right STG
Gee et al, 2012 (USA)	20	18.8	-	-	14	18.7	SIPS	Emotional faces task (Emotion discrimination)	3T Siemens Trio, Siemens Allegra & GE	MNI and ROI based approach (Harvard-Oxford Structural Atlas)	L inferior temporal gyrus, L superior frontal gyrus and middle frontal gyrus, L lateral occipital cortex, R lateral occipital cortex, R precentral gyrus, left putamen, left cerebellum
Karlsgodt et al, 2013	20 (17M, 3F)	16.85	-	-	19 (10M, 9F)	17.84	SIPS	Sternberg Style Verbal Working Memory Task	3T Siemens Allegra	MNI	Left middle frontal gyrus, right orbitofrontal cortex, cingulate gyrus, putamen, frontal pole
Niendam et al, 2013 (Sacramento, USA)	25 (14M, 11F)	16.92	35^^^	18.27	35 (19M, 16F)	17.55	SIPS	AX Continuous Performance Task (Working memory)	1.5T GE	MNI & Specific ROI in addition (Talairach)	Left precentral gyrus, bilateral middle frontal gyrus, left inferior parietal lobule, medial frontal gyrus and medial cingulate gyrus

BSABS – Bonn Scale for the Assessment of Basic Symptoms, CAARMS – Comprehensive Assessment of At Risk Mental States, CHR – Clinical High Risk, DRM – Deese-Roediger McDermott, F – Female, fMRI – functional Magnetic Resonance Imaging, HC – Healthy Controls, M – Males, MNI – Montreal Neurological Institute, PACE – Personal Assessment and Crisis Evaluation, SIPS – Structured Interview for Prodromal Symptoms, SOPS – Scale of Prodromal Symptoms, ROI – Region of Interest **Longitudinal study; ^11 CHR subjects included from Allen et al (2009); *** Multimodal imaging study with fMRI and [1]H-MRS; ^^Schizophrenia patients; ^^^First episode psychosis/schizophrenia; [#]Genetic high risk; [1]Short term; [2]Long term; ^^^^17 CHR and 15 HC reported in Broome et al, 2009; [+]17 CHR and 15 HC reported in Broome et al, 2009. [3]Non-converted and [4]Converted to psychosis

Table 2: Other relevant CHR fMRI studies included for qualitative summary

Study (Location)	Sample						Clinical Instrument	Imaging Details			Functional brain regions implicated (CHR vs HC)
	CHR	Age	Other	Age	HC	Age		fMRI paradigm	MR Scanner	Spatial normalisation template	
Morey et al, 2005 (Raleigh, USA)	10	22.6	15[1] 11[2]	24.1[1] 38.1[2]	16	28.0	SIPS, COPS	Visual Oddball Task (Attention and executive function)	1.5T Signa GE	ROI based approach*	Anterior cingulate cortex, inferior frontal gyrus, middle frontal gyrus
Benetti et al, 2009 (London, UK)	16	24.13	10^^^	25.50	14	26.04	CAARMS	Delayed Matching To Sample Test (Working memory)	1.5T Signa GE	MNI	No group differences in activation at whole brain level
Crossley et al, 2009 (London, UK)	16	-	10^^^	-	13	-	CAARMS	N Back Task (Working memory)	1.5T Signa GE	MNI	No group differences in activation in whole brain analysis
Broome et al, 2010b (London, UK)	17	24.2	10^^^	25.5	15	25.4	CAARMS	Paired associate learning task (Working memory)	1.5T Signa GE	Talairach	Right cerebellum, right precuneus, medial frontal and superior frontal gyrus with intermediate PAL task
Shim et al, 2010 (Seol, South Korea)	23	20.8	-	-	39	21.7	CAARMS	Resting state	1.5T Siemens Magnetom Avanto	MNI	DMN – Posterior cingulate cortex, bilateral anterior cingulate cortex, medial prefrontal cortex, precuneus, lateral parietal cortex TRN – bilateral dorsolateral prefrontal cortex, left supplementary area, inferior parietal lobule , middle temporal cortex
Jung et al, 2012 (Seol, Korea)	16	21.63	16	24.75	23	22.87	CAARMS	Controlled oral word association test and Resting scan (Executive function)	1.5T Siemens Avanto	ROI based approach* - MNI	No group differences in primary activation reported at whole brain level but reduced connectivity of Broca's area to right dorsolateral prefrontal cortex and left medial superior frontal cortex
Dandash et al, 2013 (Singapore)	74	21.4	-	-	35	22.8	CAARMS	Resting state	3T Siemens Magnetom	MNI	No main group differences in activation but in functional connectivity in dorsal caudate, dorsal putamen and ventral putamen
Schmidt et al, 2013[#] (Basel, Switzerland)	17	25.24	21	28.57	20	26.54	PACE	N-back task (Working memory)	3T Siemens Magnetom Verio	ROI based approach*	Superior parietal lobe and middle frontal gyrus
Fryer et al 2013	32	17.0	22[1]	22.1	54	19.5	SIPS, COPS	Sternberg Item Recognition Paradigm (SIRP) (Working memory)	3T Siemens Allegra	ROI based approach* - MNI	Medial prefrontal cortex
Pettersson-Yeo et al, 2013 (London, UK)	19	22.42	19^^^	22.42	19	23.32	CAARMS	California verbal learning test – II (Executive function)	3T Signa GE	MNI	No main group differences at whole brain level

CAARMS – Comprehensive Assessment of At Risk Mental States, COPS – Criteria for Prodromal States, PACE - Personal Assessment and Crisis Evaluation, SIPS – Structured Interview for Prodromal Symptoms, ROI – Region of Interest, MNI – Montreal Neurological Institute; [1]Early schizophrenia, [2]Chronic Schizophrenia; *Predetermined Region of Interest approach (brain regions traced manually); ^^^First episode psychosis; # - Original study data included in the quantitative review (Smieskova et al, 2011)

Table 3: Significant decreased and increased activation cluster volumes and weighted coordinates in CHR in comparison to HC (FDR corrected threshold of p<0.01); 'n' refers to the number of studies.

Sample subsets	Decreased Regional Activations in CHR	Volume (mm^3)	MNI coordinates		
			X	y	Z
Total pooled sample (n=15)	Right Inferior Parietal Lobule	800	46	-44	50
	Left Medial Frontal Gyrus	504	2	22	44
Excluding social cognition (n=12)	Right Inferior Parietal Lobule	744	46	-44	50
	Left Medial Frontal Gyrus	456	2	22	44
n-back only (n=4)	Right Inferior Parietal Lobule	264	46	-44	48
Sample subsets	**Increased Regional Activations in CHR**	**Volume (mm^3)**	**MNI coordinates**		
			X	y	Z
Total pooled ample (n=11)	Right Superior Frontal Gyrus	368	28	52	-4
	Left Superior Temporal Gyrus	256	-42	-56	26
Excluding social cognition (n=9)	Right Superior Frontal Gyrus	376	28	52	-4

Figures

Figure 1

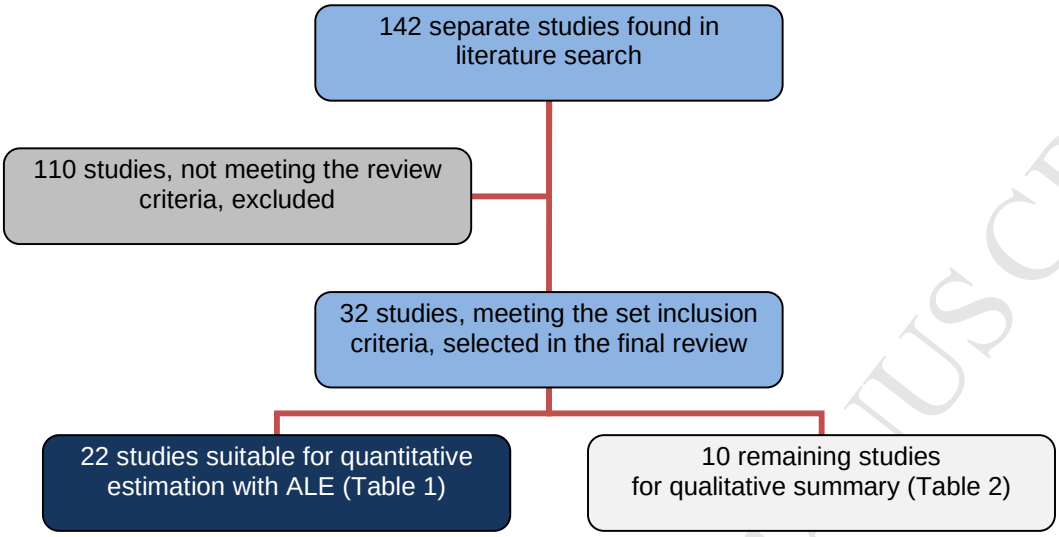
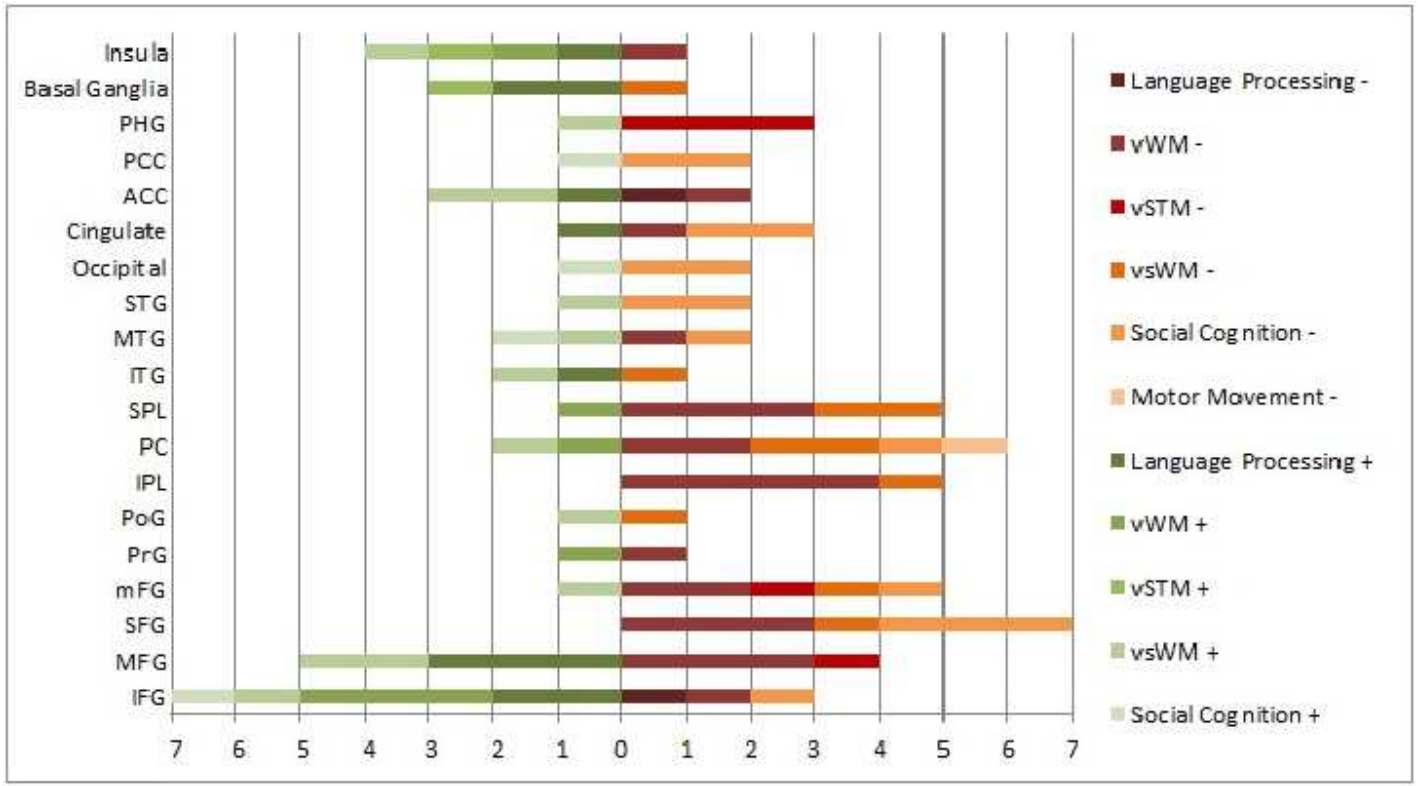
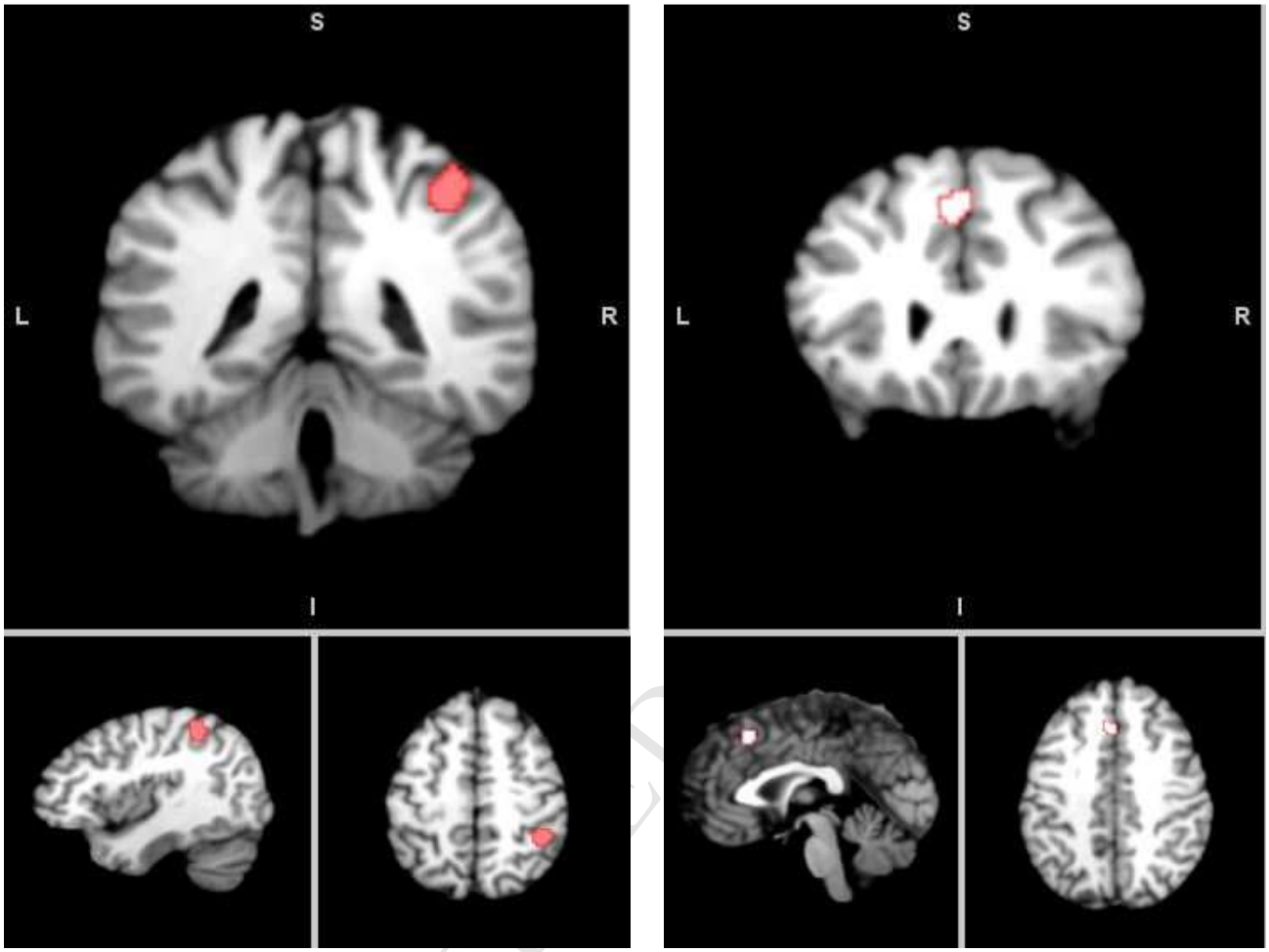


Figure 2: Qualitative representation of regional brain activation between CHR and HC across pooled studies based on fMRI paradigm



Numbers along the x axis represent the number of times a specific foci of activation (as plotted on the y axis), has been observed for one or more broad groups of cognitive paradigm across different studies; Each colour depicts a broad cluster of cognitive paradigm (language processing; vWM – verbal working memory; vSTM – verbal short term memory; vsWM – visuo-spatial working memory; social cognition; motor movement) - contrasting colours with positive and negative signs indicating hyperactivation and hypoactivation respectively in CHR in comparison to HC; IFG – Inferior Frontal Gyrus; MFG – Middle Frontal Gyrus; SFG – Superior Frontal Gyrus; mFG – Medial Frontal Gyrus; PrG – Precentral Gyrus; PoG – Postcentral Gyrus; IPL – Inferior Parietal Lobule; PC – Precuneus; SPL – Superior Parietal Lobule; ITG – Inferior Temporal Gyrus; MTG – Middle Temporal Gyrus; STG – Superior Temporal Gyrus; ACC – Anterior Cingulate Cortex; PCC – Posterior Cingulate Cortex; PHG – Parahippocampal Gyrus; '+' indicates increased activation in CHR; '-' indicates decreased activation in CHR

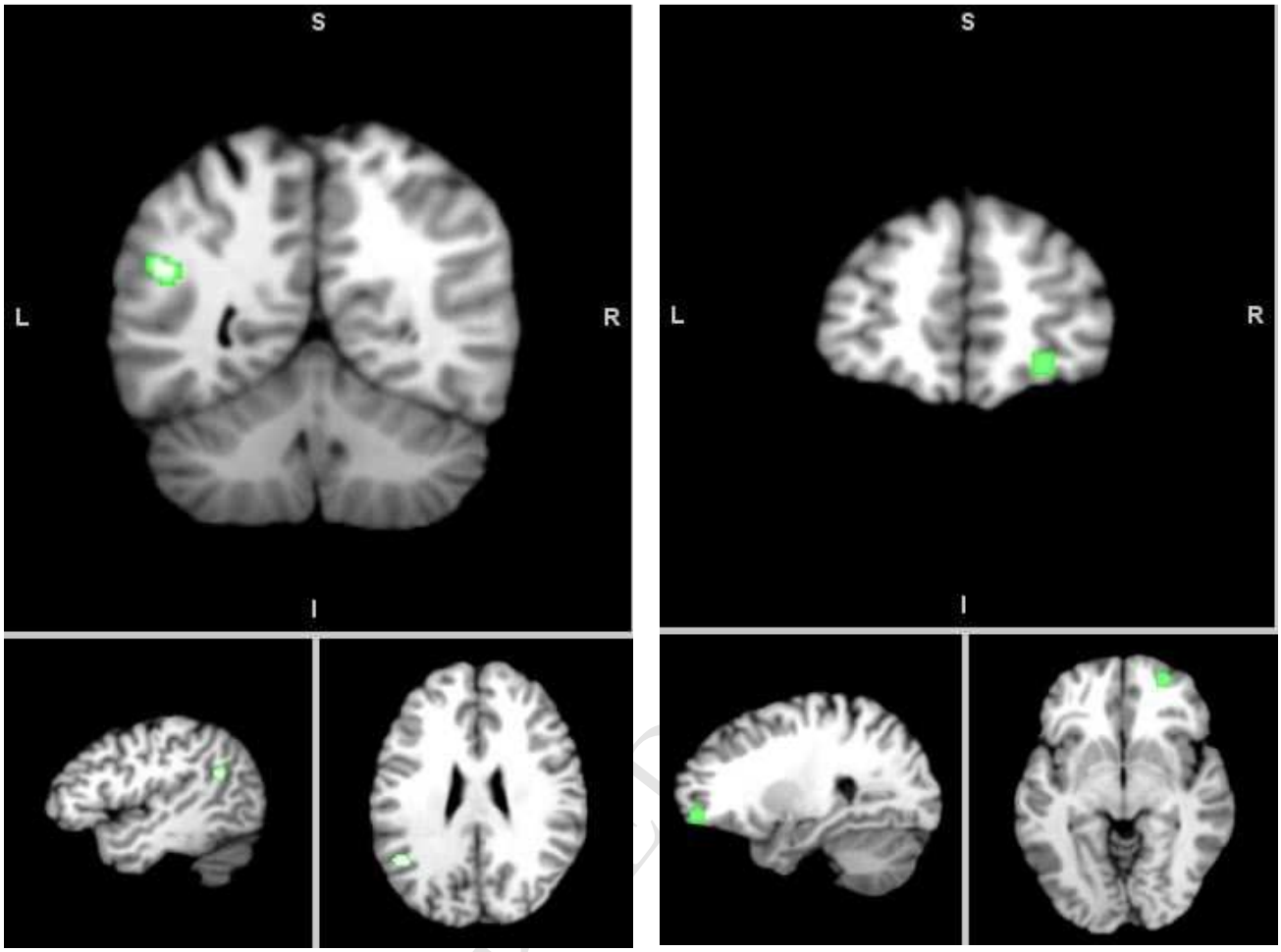
Figure 3: ALE maps showing decreased activation in CHR in comparison to controls with threshold set at p<0.01



Right inferior parietal lobule
Brodmann area 40

Left medial frontal gyrus
Brodmann area 6

Figure 4: ALE maps showing increased activation in CHR in comparison to controls with threshold set at p<0.01



Left superior temporal gyrus
Brodmann area 39

Right superior frontal gyrus
Brodmann area 10

Highlights

- Widespread fMRI dysfunction is observed in clinical high risk (CHR) for psychosis
- No consistent and conclusive evidence has emerged in fMRI literature in CHR
- Most comprehensive review, spanning almost one decade in CHR carried out with ALE
- Four dysfunctional regions spanning the frontal, parietal and temporal cortex found
- Specific neural regions and pathways as potential targets for future research

Conflict of interest

None

Contributors

Anirban Dutt was the lead author of the this study and was involved in all aspects of the project, including literature search, methods, analysis, and manuscripit write-up; Huai-Hsuan Tseng and Leon Fonville contributed to independent data extraction, and verification of graphs, analysis and results; Liang Su contributed to independent data extraction and feedback on analysis; Mark Drakesmith, John Evans and Derek Jones gave individual feedback into imaging aspects, methodology and interpretation of findings; Stan Zammit and Glyn Lewis contributed to critical review of overall methodological aspects of the study; Anthony David, the corresponding author, was also the overall supervisor of this project.

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