TITLE

Neuroimaging predictors of transition to psychosis – A systematic review and meta-analysis

Smieskova R[1,2], Fusar-Poli P[3], Allen P[3], Bendfeldt K[2], Stieglitz RD[1], Drewe J[4], Radue EW[2], McGuire PK[3], Riecher-Rössler A[1], * Borgwardt SJ[1,2,3]

[1] Psychiatric Outpatient Department

[2] Medical Image Analysis Centre

[4] Dep. Clinical Pharmacology

University Hospital Basel

Petersgraben 4

CH-4031 Basel

Switzerland

[3] Section of Neuroimaging

King's College London

Institute of Psychiatry, PO67

De Crespigny Park

London SE5 8AF

UK

ABSTRACT

Objectives: In early stage psychosis research is the identification of neurobiological correlates of vulnerability to schizophrenia an important hurdle.

Methods: We conducted a systematic review of the neuroimaging publications on high-risk subjects with subsequent transition to psychosis (HR-T) and conducted a meta-analysis using the Cohen's d.

Results: Out of 30 identified studies 25 met the inclusion criteria. sMRI studies showed small to medium effect sizes of decreased prefrontal, cingulate, insular and cerebellar gray matter volume in HR-T compared to high-risk subjects without transition (HR-NT) and reduced temporal cortex in first episode (FE) of psychosis subjects compared to HR-T.

Compared to HR-NT, HR-T subjects showed in functional imaging studies reduced brain activation in prefrontal cortex, reduced neuronal density, increased membrane turnover in frontal and cingulate cortex and decreased availability of serotonine receptors in prefrontal cortex with medium to large effect sizes.

Conclusions: Despite methodological differences between studies, structural and neurochemical abnormalities in prefrontal, anterior cingulate, medial temporal and cerebellar cortex might be predictive for development of psychosis within HR subjects.

Keywords: psychosis, schizophrenia, high-risk, at risk mental state, transition, brain, neuroimaging, systematic review, meta-analysis, fMRI, sMRI, PET, MRS

1. INTRODUCTION

Over the past 15 years early clinical intervention in schizophrenia has become a major objective of mental health services. While in the beginning, early detection centres focused on the early diagnosis of first episode (FE) of schizophrenia, in later years these centres have also started preventive interventions. Such strategies are aimed at identifying and treating patients before the criteria for a DSM-III R or DSM-IV schizophrenia diagnosis are fulfilled and prior to the onset of frank psychosis, a period of time broadly termed as high-risk (HR) state for psychosis (for review see (Riecher-Rossler et al., 2006)).

Evidence for a high-risk state is emerging, in part because schizophrenia may result from a genetic predisposition (Lawrie et al., 2008) and/or gene-neurodevelopmental interaction (DeLisi, 2008; Pantelis et al., 2005) leading to defective connections of critical brain regions and cytoarchitectural abnormalities which could explain the variety of clinical, neurobiological and neuropsychological features occurring before the onset of psychosis (Cannon, 2005; Tsuang et al., 2000).

1.1 High-risk research paradigms

Research on the early phase of the disorder may provide important clues to the mechanisms underlying schizophrenia, thereby facilitating early diagnosis and treatment strategies. In order to investigate the characteristics of liability to psychosis, two high-risk research paradigms have recently been developed. Endorsing the genetic high-risk approach, putative endophenotypes can be evaluated for association with genetic risk for schizophrenia by comparing the unaffected co-twins of patients

or the unaffected relatives of patients with normal controls (Baare et al., 2001; Hulshoff Pol et al., 2004; Job et al., 2003; Johnson et al., 2003; Lawrie et al., 1999; Lawrie et al., 2002; van Erp et al., 2004; van Haren et al., 2004; Whyte et al., 2006).

Alternatively, 'close in' i.e. clinical high-risk approaches are able to identify a group at ultra high-risk of psychosis with higher transition rates than those observed in studies purely based on genetic inclusion criteria (Cornblatt et al., 2002; McGlashan and Johannessen, 1996; Pantelis et al., 2007; Yung et al., 1998). The latter approach, focusing on individuals who are considered to be at increased risk for psychotic disorders, is based primarily on the presence of clinical symptoms. The strategy aims at identifying neural changes occurring prior to the onset of psychosis and may improve our ability to predict schizophrenia outcomes based on the combined perspectives of both neural and clinical characteristics observed at the baseline assessment.

HR subjects have been shown to present attenuated positive, brief limited intermittent (Riecher-Rossler et al., 2007; Riecher-Rossler et al., 2009; Yung et al., 2004), and negative (Lencz et al., 2004; Riecher-Rossler et al., 2009) psychotic symptoms and mild cognitive deficits (Brewer et al., 2006; Riecher-Rossler et al., 2009). Compared to a healthy population, they have a significantly greater probability of developing the illness (Riecher-Rossler et al., 2007; Riecher-Rossler et al., 2009; Yung et al., 1998), suggesting that specific aspects of prodromal symptoms may represent vulnerability markers for developing schizophrenia (Morey et al., 2005). However, there is a high level of heterogeneity among inclusion criteria for the high-risk state. Hence, the term 'at-risk mental state' (ARMS) has been suggested instead of the term 'prodromal', to delineate a sub-threshold syndrome that confers high - but not inevitable - risk for development of psychotic disorder in the near future (Yung et al., 1998).

1.2 Neuroimaging studies of liability to psychosis

Over the past decade, neuroimaging techniques have been employed to explore the neurobiological correlates of an increased liability to psychosis. These methods include structural (sMRI) and functional (fMRI, MRS and PET) approaches. Structural neuroimaging studies from FE schizophrenia subjects reported small reductions in global and regional brain volumes at initial presentation (Steen et al., 2006), and volume loss over time in those patients who have a deteriorating clinical course (DeLisi et al., 1997; Ho et al., 2003; Kasai et al., 2003; Lieberman et al., 2001). These volume reductions in FE compared to HC subjects resemble observations from meta-analytic reviews of chronic schizophrenics compared to HC subjects (Glahn et al., 2008; Honea et al., 2005; Vita et al., 2006; Wright et al., 2000). Additionally, functional imaging studies indicate that the neurofunctional abnormalities during cognitive tasks are qualitatively similar but less severe in HR subjects compared to FE patients (Fusar-Poli et al., 2007). However, the onset and the time-course of structural and functional alterations are mostly unknown. Indeed, it is critical to the understanding of the pathogenesis of these brain changes to clarify their onset and the dynamic neurobiological processes underlying the transition from a high-risk state to full-blown psychosis.

To address the neurobiological correlates of transition to psychosis, here we have reviewed cross-sectional and longitudinal structural and functional imaging studies that have compared high-risk subjects with (HR-T) and without (HR-NT) later transition to psychosis. With the combination of structural and functional meta-

analytical results we intend to characterise predictive neuroanatomical and neurofunctional abnormalities underlying the transition to psychosis.

Our hypotheses were:

1. HR-T subjects would show, even before transition to psychosis, volumetric abnormalities relative to HR-NT ones qualitatively similar to those in patients with FE schizophrenia.

2. Neuroanatomical and neurofunctional abnormalities in HR-T and FE subjects would be found in similar brain regions (i.e. prefrontal, cingulate and medial temporal cortex), but differently strong pronounced.

2. METHODS

To achieve the high standard of reporting we have adopted 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) guidelines (Minzenberg et al., 2009), the revised QUOROM Statements (Quality Of Reporting Of Meta-analyses), because our included studies are mostly case-control studies. We then performed the quantitative analysis on included studies.

2.1. Selection procedures

2.1.1. Search strategy

Electronic searches were performed in the PUBMED database using the following search terms: psychosis, schizophrenia, at-risk mental state, high-risk, neuroimaging, brain imaging, magnetic resonance imaging, MRI, functional magnetic resonance, fMRI, structural magnetic resonance imaging, sMRI, positron emission tomography, PET, proton magnetic resonance spectroscopy, MRS. Two reviewers (RS, SB) independently reviewed the database and extracted the data in order to avoid bias or error in the selection of articles and by the extraction of data from studies.

In addition we carefully searched the reference lists of the included articles identified in the original search. All reports published until September 2009 were included, without any language restriction though all included papers were in English.

2.1.2. Selection criteria

Initially, we performed a systematic review and meta-analysis including a description of all studies employing neuroimaging to investigate brain structure or function in high-risk populations. Then, we hand-searched the papers in order to select studies meeting our inclusion criteria: (a) be an original paper in a peer-reviewed journal (b) have examined subjects at high-risk of psychosis (as defined in paragraph 2.2.) using functional or structural neuroimaging techniques (c) have divided the group of high-risk subjects into subgroups of HR-T and HR-NT. Imaging studies of high-risk subjects that did not perform 'transition-versus-non-transition-contrasts' were not included. Almost all of included studies are case-controlled studies and they had to have control subjects that were matched for age and sex. There is one pilot study (Pantelis et al., 2003) and three following studies (Sun et al., 2009; Thompson et al., 2007; Walterfang et al., 2008) based on the same group of patients without a control group of healthy subjects. We have excluded studies that involved participants of less than 14 years of age, subjects with other neurological or psychiatric disorders, and/or substance abuse disorder (see paragraph 3.2). When the data from a single subject sample were reported in separate publications, these were treated as single studies. Conversely, a publication that reported two forms of different imaging data from the same subjects was considered as two studies.

2.2. Recorded variables

The recorded variables for each article included in the review were: imaging centre where the study was performed, type of design or task, gender, mean age of

participants, duration of follow-up, transition rate, type of imaging analysis, exposure to medications. The primary outcomes of interest were global/regional volumes for structural and global/regional activity for functional imaging studies, as well as metabolic ratios of cerebral tissue compounds for MRS and binding potential of cerebral receptors for PET studies. There is the intracranial volume (ICV) as a sum of the volume of all voxels designated as gray matter volume, white matter volume plus cerebrospinal fluid and the whole brain volume (WBV) as a sum of gray matter plus white matter volume (Courchesne et al., 2000) recorded in the table 4.

Results were comprehensively reported in different tables to assist the reader in forming an independent view on the following discussion. We have included one summary table of all reviewed studies (table 2), and tables illustrating the results of structural (table 3) and functional studies (table 5).

2.3. Effect sizes

When sufficient information was provided in a study to assess the significance of the results (e.g., presence of means and standard deviations, p value, F-value), we have calculated the effect size. The effect size is a dimensionless number that facilitates the integration of findings across the studies that used different types of measurements. It is related to the choice of whether or not greater reliance should be placed on studies carried out on larger samples. We have chosen an estimator corrected for the number of subjects included in each study using Cohen's d statistic (Cohen, 1992), because a lot of fMRI or sMRI studies included small numbers of subjects. When the power of a study is insufficient to show statistically significant differences between or within samples or populations type II errors occur. The effect sizes better explain differences

in the population and whether these differences might merit further study. All calculated Cohen's d values are based on baseline data from both cross-sectional and longitudinal studies. Effect size (indexed 'd' according to Cohen's scheme (Cohen, 1992)) means 'the degree to which a phenomenon is present in the population (Cohen, 1988). The value of Cohen's d stands for either negligible effect (>= -0.15 and <.15), small effect (>=.15 and <.40), medium effect (>=.40 and <.75), large effect (>=.75 and <1.10), very large effect (>=1.10 and <1.45) or huge effect >1.45. Such methodological approach has been used in previous meta-analyses of neuroimaging studies (Fusar-Poli et al., 2007).

2.4. Risk of bias in individual studies

Publication bias reflects the increased likelihood of a study being published when the study has a positive result. Thus an intrinsic bias towards a positive result could be incorporated into the study, because fewer negative or equivocal studies exist in the literature (Callcut and Branson, 2009). We included three studies (Thompson et al., 2007; Wood et al., 2005; Yucel et al., 2003) with negative results regarding the difference between HR-T and HR-NT. All our included studies were published in peer-reviewed journals suggesting high quality of published data and excluding the possible methodological bias. Although the studies differ methodologically, we did not found any difference in outcome-level assessment of risk of bias.

3. RESULTS

3.1. Inclusion criteria for subjects at high-risk for psychosis

Neuroimaging studies published in current literature included different high-risk samples: (a) genetic high-risk subjects (a1) monozygotic and dizygotic twins discordant for schizophrenia (non-psychotic twin) (a2) subjects with at least two first- or second-degree relatives of patients affected with psychosis (Hodges et al., 1999; Johnstone et al., 2000), (b) clinical high-risk subjects (b1) subjects at ultra high-risk (UHR) and (b2) with an at-risk mental state (ARMS) (Yung et al., 2004) (Riecher-Rossler et al., 2007) (b3) subjects with 'basic symptoms' (e.g. thought and perception disturbances) (Klosterkotter et al., 2001). According to recent data, although the risks for psychosis and associated abnormalities are higher in high-risk samples than in the general population, they are not the same across these different groups: monozygotic twins have a 40–50% concordance rate for the illness over lifetime (Tsuang et al., 2002), first-degree relatives of schizophrenia patients have approximately a 10-fold increased risk for later illness compared to non-relatives over lifetime (Chang et al., 2002), while in clinical high-risk subjects the probability to develop psychosis ranges from 16% within 2 years (Yung et al., 2008) and 41% (ARMS) (Yung et al., 2003; Yung et al., 2007) up to 54% (Criteria for Prodromal Syndromes - COPS) (Miller et al., 2002) within one year (for review see (Cannon et al., 2007)), or 49% within 9,6 years (Basic symptoms - Cologne Early Recognition (CER) Project) (Klosterkotter et al., 2001).

Finally, it is worth mentioning schizotypal personality disorder, which is characterized, like schizophrenia, by positive or psychotic-like symptoms and negative or deficit-like symptoms (Siever and Davis, 2004). Although the transition rate to psychosis in such groups is still under discussion (Bedwell and Donnelly, 2005), schizotypy symptoms in subjects with a genetic risk for schizophrenia or in those with a functional decline (ARMS) are clearly associated with an increased risk for developing a psychotic episode (Siever et al., 2002).

Selection criteria for clinical HR subjects are reported in table 1 according to the differences among the centers for early detection of psychosis. Two well established centers from the English-speaking area – *Personal Assessment and Crisis Evaluation clinic* (PACE) in Melbourne and *Outreach And Support In South London* clinic (OASIS) in London - have used the instrument called *Comprehensive Assessment of Symptoms and History* (CAARMS) (Yung et al., 2005) to assess the Attenuated psychotic symptoms (APS), Brief limited psychotic symptoms (BLIPS) and trait + state risk factor (Yung et al., 1998) in the high-risk population. The same criteria with the newly developed shorter *Basel Screening Instrument for Psychosis* (BSIP) (Riecher-Rossler et al., 2008; Riecher-Rossler et al., 2007) were assessed in Basel in the Early Detection of Psychosis Clinic (FEPSY). The German research network on schizophrenia (GRNS) in Bonn, Düsseldorf, Cologne and Munich working with the ERIRAOS (Maurer and Hafner, 2007) - *Early Recognition Inventory* based on *Interview for the Retrospective Assessment of the Onset of Schizophrenia* (IRAOS) (Hafner et al., 1992) and *Bonn Scale for Assessment of Basic Symptoms* (BSABS) (Klosterkotter et al., 2001) used the same criteria of *Brief Psychiatric Rating Scale* (BPRS) and *Comprehensive Assessment of Symptoms and History* (CASH).

TABLE 1 ABOUT HERE

3.2. Number of identified studies

As the approach of the selective comparison of HR-T versus HC, HR-NT and first episode (FE) patients is a relatively new one, all of the 30 studies initially identified, were published between 2002 and 2009. Three studies (Job et al., 2006; Koutsouleris et al., 2009a; McIntosh et al., 2007) were eliminated because they did not fulfil the *a priori* selection criteria (for included and excluded studies see Figure 1). The remaining studies were grouped according to centre/population of the study (clinical HR with an ARMS: Melbourne, Basel, Munich, Bonn; genetic HR: Edinburgh), neuroimaging technique employed (structural/functional), design of the study (cross-sectional/longitudinal), and cognitive task (Figure 1, Table 2). The systematic review of the literature uncovered 20 structural imaging studies (16 MRI, two gyrification index (GI), two cortical pattern matching (CPM)) and five functional imaging studies (two fMRI, two Magnetic Resonance Spectroscopy (MRS) and one Positron Emission Tomography (PET)). The total number of subjects included in the present review encompassed roughly 385 HR subjects altogether, of whom 95 subsequently made a transition to psychosis (HR-T), 290 healthy controls (HC) and 211 first episode (FE) patients. The flowchart of the selection procedure with the included/excluded studies is summarized in Figure 1 and was created on the template of the PRISMA flow diagram (Minzenberg et al., 2009) available on the web site http://www.prisma-statement.org/ .

3.3. Risk of bias within studies

Within our included studies we have not found any differences in risk of bias.

FIGURE 1 AND TABLE 2 ABOUT HERE

The results of our systematic review and meta-analysis are summarized below with respect to structural (3.3) and functional (3.4.) imaging findings.

3.4. Structural magnetic resonance imaging studies of individuals at high-risk of psychosis

Two publications (Goghari et al., 2007; Witthaus et al., 2008) were excluded, because each of them comprised only one patient, who made the transition to psychosis.

Across the selected imaging database we uncovered different structural neuroimaging methods: seven studies used voxel-based morphometry (VBM), nine studies used region of interest (ROI), two used studies gyrification index (GI) and further two used Cortical Pattern Matching (CPM).

GI measures the ratio of the entire cortical (inner) contour of the brain to the superficially exposed or outer contour and increases proportionally with the number and complexity of gyri (Zilles et al., 1988). The group of Harris et al. have used hand-traced GI methodology in an older study, and later an automated GI (A-GI) methodology of prefrontal cortex folding (Harris et al., 2007; Harris et al., 2004). CPM encodes both gyral patterning and gyral-matter variation (Thompson et al., 2004). This is an advanced brain registration technique that can achieve accurate

anatomical correspondence between surfaces (Sun et al., 2009). One VBM study (Walterfang et al., 2008) determined whether changes in the gray matter are accompanied by changes in the white matter.

TABLE 3 ABOUT HERE

3.4.1. Structural magnetic resonance imaging studies using voxel-based methods

3.4.1.1. Cross-sectional VBM studies of gray matter abnormalities

The first VBM study examining gray matter volumes of HR-T versus HR-NT found less gray matter volume in right hippocampal, parahippocampal and cingulate cortex, lateral temporal and inferior frontal cortex at baseline (Pantelis et al., 2003).

Studies by our own group showed that compared to HC, HR-T subjects had smaller gray matter volumes in the cingulate gyrus, precuneus and paracentral lobule bilaterally, the latter extending into the left superior parietal lobule (Borgwardt et al., 2007a). At the same time there were regions with greater gray matter volume in right parahippocampal and supramarginal gyri and inferior temporal gyrus. These latter volumetric increases were evident already 1-2 years before transition to psychosis.

When compared to HR-NT, HR-T subjects showed reduced gray matter volume in the superior temporal and inferior frontal gyrus and insula (Borgwardt et al., 2007b). Koutsouleris et al. (Koutsouleris et al., 2009b) also found frontal volumetric reductions predominantly in the anterior cingulate, prefrontal and orbitofrontal cortex bilaterally in HR-T subjects compared to the HR-NT patients.

Cross-sectional VBM studies thus found identically decreased gray matter volume in frontal, cingulate and temporal cortex in HR-T compared to HR-NT.

3.4.1.2. Longitudinal VBM studies of gray matter abnormalities

Other studies focused on the longitudinal changes underlying the onset of psychosis. In a subgroup of already mentioned sample Pantelis et al. studied also progressive changes and found gray matter reductions in the left hemisphere in medial temporal, orbitofrontal, cingulate cortex and cerebellum (Pantelis et al., 2003).

Borgwardt et al. (Borgwardt et al., 2008) reported orbitofrontal, superior frontal, inferior temporal, medial and superior parietal cortex and cerebellar gray matter reductions in HR-T patients compared to HR-NT.

The only genetic high-risk longitudinal study (Job et al., 2005) found lower gray matter density in left inferior temporal gyrus, uncus and right cerebellum over follow-up between HR-T and HR-NT subjects (Job et al., 2005).

The greater brain surface contraction in the right prefrontal region was another progressive change seen in HR-T compared HR-NT (Sun et al., 2009). Takahashi and colleagues found longitudinal gray matter volume reduction in superior temporal gyrus left in HR-T compared to HR-NT (Takahashi et al., 2009b).

The most consistent results of progressive studies with HR-T versus HR-NT comparison included temporal, frontal and cerebellar gray matter reduction.

3.4.1.3. VBM studies comparing FE and HR-T

The differences in gray matter volumes between FE schizophrenia patients and HR-T were evaluated only in three studies (Borgwardt et al., 2007a; Phillips et al., 2002; Takahashi et al., 2009b). Cross-sectional comparisons showed volume reductions in the superior temporal gyrus in FE subjects as compared to HR-T, HR-NT and HC. Both FE and HR-T showed progressive reduced gray matter volume in superior temporal regions (Takahashi et al., 2009b).

According to a study by our own group, there were gray matter volume reductions in FE as compared to HR-T along the superior, middle and inferior temporal gyrus and the region of larger gray matter volume in the right lentiform nucleus (Borgwardt et al., 2007a).

3.4.1.4. Other studies

Walterfang et al (Walterfang et al., 2008) focused on white matter abnormalities in HR population using VBM. They found that compared to HR-NT, HR-T subjects showed larger white matter volumes in the left frontal lobe. Longitudinally, HR-T revealed a reduction in white matter volume in a region of the left fronto-occipital fasciculus (Walterfang et al., 2008).

Harris and colleagues measured the hand-traced gyrification index and found increases in right prefrontal lobe GI values in HR-T individuals compared to HR-NT (Harris et al., 2004). Interestingly, the disproportionately high right prefrontal GI distinguishes the HR-T from other groups (HR-NT, HC, FE) and can predict schizophrenia several years before, while white matter volume can not (Harris et al., 2007).

3.4.2. Structural magnetic resonance imaging studies using region-of-interest (ROI) approaches

ROI approaches have also been used in a number of brain morphology studies of the HR population. They often used various procedures to describe the brain areas, which are either manually or automatically delineated. Despite of this we discuss the results from ROI studies according to the investigated regions.

Medial temporal region

Here we present findings related to hippocampal and amygdala volumes as a part of the medial temporal lobe (Shenton et al., 2001). Volumetric hippocampal measurements were provided in five MRI studies. An early cross-sectional study by Phillips et al. (Phillips et al., 2002) reported smaller hippocampal volumes in HR-T compared to HR-NT. Similar results have been observed in FE patients compared to HR-T while no differences were found between HR-T and HC (Phillips et al., 2002).
In contrast, two larger studies (Velakoulis et al., 2006; Wood et al., 2005) reported no differences in hippocampal volume between HR-T and HR-NT. Bühlmann et al. (Buehlmann et al., 2009) also failed to find volumetric differences in the hippocampus in HR-T vs. HR-NT albeit in a smaller sample. No relationship between cortisol plasma levels and hippocampal volumes was observed in the neurobiological model of stress in cross-sectional study by Thompson et al. (Thompson et al., 2007).
Another cross-sectional study showed no differences in amygdala volume among HR-T and HR-NT, HC and FE patients (Velakoulis et al., 2006).

Cingulate cortex

The anterior cingulate cortex (ACC) was investigated in three studies from the Melbourne group (Fornito et al., 2008; Wood et al., 2005; Yucel et al., 2003). Yücel (Yucel et al., 2003) found no differences in any of the ACC surface morphological measures between HR-T and HR-NT. Another study showed a trend towards left hemispheric reduced paracingulate sulcus folding and frequent cingulate sulcus interruptions in HR subjects, with no differences between HR-T and HR-NT subjects, in line with the above findings (Wood et al., 2005).

Fornito (Fornito et al., 2008) used a surface-based anterior cingulate parcelation technique and reported that regional thinning of the ACC is a significant predictor of the time to psychosis onset. They found a bilateral thinning of the rostral paralimbic ACC in HR-T compared to HC.

Insular cortex

We uncovered VBM studies (Borgwardt et al., 2007b; Pantelis et al., 2003) showing insular gray matter reductions in the HR-T compared to the HR-NT. These findings were parallel to the cross sectional and longitudinal insular gray matter abnormalities observed within the HR group (Takahashi et al., 2009a).

Pituitary

Garner (Garner et al., 2005) reported that within the HR subjects the baseline pituitary volume was a significant predictor of future transition to psychosis. HR-T subjects

had significantly larger pituitary volumes than HC. At the same time HC had larger pituitary volume than HR-NT. Thompson et al. found no relationship between cortisol plasma levels or number of glucocorticoid receptors and pituitary volume, suggesting that impairment in hypothalamic-pituitary-adrenal axis may be detectable later in the disease process (Thompson et al., 2007).

3.4.3. Meta-Analysis of structural magnetic resonance imaging studies

We have calculated Cohen`s d in 11 of 20 included sMRI studies (Table 4). The study by Walterfang et al. (Walterfang et al., 2008) was excluded as it focuses on the white matter changes. Three studies without control group (Pantelis et al., 2003; Sun et al., 2009; Thompson et al., 2007) have considerably influenced the direction of subsequent research and were included, albeit we could not calculate Cohen`s d. Effect size was not calculated in another two studies with no significant differences between HR-T and HR-NT (Wood et al., 2005; Yucel et al., 2003) and in two another studies (Borgwardt et al., 2008; Job et al., 2005) as well.

With small to medium effect sizes, whole brain volumes and/or global gray matter volumes were consistently increased in HR-T relative to HR-NT but also compared to FE patients (Borgwardt et al., 2007a; Borgwardt et al., 2007b; Harris et al., 2007; Harris et al., 2004; Takahashi et al., 2009a; Takahashi et al., 2009b; Velakoulis et al., 2006). This increase is also seen in comparison of HR-T to the HC with medium effect size with the exception of one study reporting a small effect size of decrease of gray matter volume in HR-T compared to HC (Borgwardt et al., 2007b) (table 4).

Compared to HR-NT, HR-T subjects showed relatively reduced regional gray matter volume in the insula (Borgwardt et al., 2007b; Pantelis et al., 2003; Takahashi et al.,

2009a), anterior cingulate (Fornito et al., 2008; Pantelis et al., 2003), prefrontal cortex (Borgwardt et al., 2008; Pantelis et al., 2003; Sun et al., 2009) and cerebellum (Borgwardt et al., 2008; Job et al., 2005; Pantelis et al., 2003) with small to large effect sizes (table 4). These regions were the most consistently abnormal brain regions associated with later transition to psychosis. Through that two ROI-studies found no differences in anterior cingulate among HR individuals (Wood et al., 2005; Yucel et al., 2003) and one study found increased gray matter volume in right prefrontal cortex in HR-T compared to HR-NT (Harris et al., 2004).

TABLE 4 ABOUT HERE

3.5. Functional neuroimaging and neurochemical studies of individuals at high-risk for psychosis

We uncovered a few functional neuroimaging studies employing different imaging methods.

The Edinburgh group employed the *Hayling Sentence Completion Task* (HSCT) and the '*Theory of Mind*' paradigm (Marjoram et al., 2006; Whalley et al., 2006). One positron emission tomography (PET) study (Hurlemann et al., 2008) had focused on the availability of the cerebral serotonin (5-HT) receptor in naive HR subjects. Finally, two proton magnetic resonance spectroscopy (MRS) studies (Jessen et al., 2006; Wood et al., 2003) measured N-acetyl aspartat (NAA), cholin (Cho) and creatine (Cr) as marker for neuronal density, function and cell metabolism respectively.

TABLE 5 ABOUT HERE

3.5.1. Functional MRI (fMRI) studies

Both studies from this subsection have investigated cross-sectional abnormalities between HR-T and HR-NT subjects.

Decreased activation in anterior cingulate cortex and increased activation in left parietal lobe were described in genetic HR-T relative to HC in a prospective cross-sectional study using the HSCT (Whalley et al., 2006). Compared to HR-NT, HR-T subjects showed smaller increases in activation with increasing task difficulty in the right lingual gyrus (Whalley et al., 2006). In a 'Theory of Mind' imaging study, which requires ability to understand a joke, Marjoram et al. (Marjoram et al., 2006) investigated prefrontal cortex activation associated with memory and executive functioning tasks. Compared to HR-NT, HR-T showed less neural activation in the middle frontal gyrus right (Marjoram et al., 2006).

3.5.2. Other functional neuroimaging studies (PET, MRS)

Hurlemann et al. investigated abnormalities in serotonin subtype 2A receptor (5-HT_{2A}R) in prefrontal cortex using PET. 5-HT_{2A}R binding potential (BP) in right caudate nucleus was significantly reduced in HR-T compared to HC. Furthermore, HR-T compared to HR-NT had the most significant decreases in 5-HT_{2A}R BP in the insular cortex (Hurlemann et al., 2008).

Using MRS, the HR-T subjects showed reduced NAA/Cho ration as compared to HR-NT, suggesting an impaired neuronal density and function. Jessen et al. (Jessen et al., 2006) showed a significantly lower NAA/Cho and higher Cho/Cr in HR-T compared to HR-NT in the anterior cingulate gyrus and a trend towards a reduction of NAA/Cho in the frontal lobe. Reductions of NAA in the left prefrontal lobe and ACC may represent a vulnerability to schizophrenia and elevated levels of cholin containing compounds in the anterior cingulate gyrus may predict conversion to frank psychosis (Jessen et al., 2006).

In a second MRS study, Wood et al. (Wood et al., 2003) investigated medial temporal and dorsolateral prefrontal regions but found no significant differences in NAA, Cr and Cho levels within the HR sample (HR-T vs HR-NT). However, there was a trend toward a significantly higher NAA/Cho in the HR-T compared to HR-NT in the medial temporal region (Wood et al., 2003).

3.5.3. Meta-Analysis of functional imaging studies

Cohen`s d calculated from functional imaging data showed altered activation of the brain regions (table 6), where gray and white matter changes were observed (table 4), but in other brain regions as well.

fMRI studies have found less activation in HR-T compared to HR-NT in prefrontal cortex with medium effect size (Marjoram et al., 2006), and in cingulate cortex and in occipital lobe (Whalley et al., 2006).

Conversely, MRS studies showed a huge effect size of the reduction of neuronal density and increased membrane turnover in cingulate (Jessen et al., 2006). They also proved an increase of neuronal density in medial temporal cortex (Wood et al., 2003)

in HR-T compared to HR-NT. The availability of 5-HT_{2A} receptors was significantly decreased as we found a huge effect size in HR-T compared to HR-NT in prefrontal cortex (Hurlemann et al., 2008).

TABLE 6 ABOUT HERE

4. DISCUSSION

With this study we aimed at reviewing the neuroimaging predictors of transition to psychosis. We were searching neuroanatomical and neurofunctional abnormalities of HR-T in relation to HR-NT, HC and FE. According to our first hypothesis, structural neuroimaging studies revealed volumetric abnormalities in temporal, cingulate, insular, prefrontal cortex and in cerebellum in HRT already before transition to psychosis compared to HR-NT. The present meta-analysis showed small to medium effect size of increased whole brain volume and total gray matter volume in the group of the HR-T as compared to the HR-NT, but interestingly also compared to the FE and to the HC. This effect of increased whole brain volume could indicate a dynamic process during the transition phase to psychosis, presumably affecting various cortical areas at approximately identical time points.

Functional neuroimaging studies showed reduced brain activation in prefrontal cortex, reduced neuronal density, increased membrane turnover in frontal and cingulate cortex and decreased availability of serotonine receptors in prefrontal cortex with medium to large effect sizes. The localization of neurofunctional abnormalities between HR-T and HR-NT corresponds to the region-specific neuroanatomical abnormalities revealed by structural neuroimaging studies. These neurofunctional

abnormalities could delineate a pathological process in the affected brain regions as well as a compensatory process to volumetric region-specific reductions in gray or white matter.

4.1. Brain structural and neurofunctional abnormalities associated with transition to psychosis

This review and meta-analysis shows that the transition from a prodromal state to the onset of psychosis (as compared between HR-T and HR-NT) is associated with patterns of subtle gray matter abnormalities within frontal and temporal cortices, the limbic system and the cerebellum (Borgwardt et al., 2007b; Job et al., 2003; Meisenzahl et al., 2008; Pantelis et al., 2003).

Our review added evidence to the available literature by showing that structural abnormalities in medial temporal, prefrontal, anterior cingulate and insular cortex might be most predictive for a development of psychosis. At least some of the cortical gray matter abnormalities known in psychotic patients seem to occur during the acute process of transition to psychosis. While some subtle alterations in brain structure (reductions in cingulate, insular and prefrontal regions) (Borgwardt et al., 2007b; Koutsouleris et al., 2009b; Pantelis et al., 2003) seem to occur already in the prodromal stage, other brain structural changes (i.e. superior temporal gyrus volume reductions) (Takahashi et al., 2009b) found in psychoses may emerge as psychosis develops.

Although fMRI did not reveal significant effect sizes, the present findings of decreased activation in prefrontal areas and increased activation in connected brain

regions could indicate a compensatory mechanism. Contemporary meta-analysis of 41 executive fMRI studies of schizophrenia patients showed reduced activation in a similar neural network in prefrontal cortex, and anterior cingulate as in healthy controls, and compensatory increased activation in other prefrontal areas (Minzenberg et al., 2009).

MRS and PET studies have shown a huge effect size of the reduction of neuronal density and increased membrane turnover in frontal lobe and cingulate as well as decreased availability of serotonine receptors in prefrontal cortex in HR-T compared to HR-NT.

Although we have found structural gray matter alterations and neuronal activity reduction in prefrontal and cingulate cortex and reduction in neuronal activity in occipital lobe in HR-T versus HR-NT, it is difficult to describe their relationship. Similarly, the reductions in white matter volume in the left fronto-occipital fasciculus (Walterfang et al., 2008) were found hand in hand with the reduction in gray matter volume in orbito-frontal, cingulate and parahippocampal areas (Pantelis et al., 2003) longitudinally in identical HR-T versus HR-NT population.

These observations are of great relevance and may be useful in filling the gap between basic and clinical neuroscience. In fact, the researchers have attempted to find reliable MRI-based correlates of prediction to the psychosis combining longitudinal changes in gray matter alterations with other clinical and cognitive predictive measures (Job et al., 2006). A recently published study (Koutsouleris et al., 2009a) has distinguished HR subjects from HC as well HR-T from HR-NT by using advanced analysis methods such as the support vector machines (SMVs). They have achieved fairly high accuracy, sensitivity and specificity in their prediction to psychosis based on the

pattern of gray matter volume reductions in temporal and prefrontal cortex, in the thalamus and the cerebellum in HR-T versus HR-NT.

Neuroimaging may be able to decompose state and trait variables during the early phases of psychosis. Structural and functional neuroimaging (and the combination of imaging techniques) have the potential to delineate the time course of brain abnormalities in the evolution of psychosis. The observation that transition to psychosis is associated with specific structural and neurofunctional abnormalities raises the possibility that multimodal neuroimaging techniques could be used to identify the core pathophysiological changes underlying the onset of psychosis (Fusar-Poli et al., 2009).

4.2. Methodological issues and limit of this study

Limits of the present review and meta-analysis are well acknowledged. The methods and extent of detailed information to define regions of interest vary widely between the studies, preventing accurate comparison. In addition we uncovered a large difference in secondary variables across studies (i.e. gender, medication, comorbidities), which may have played a confounding role. In particular, the relatively small number of fMRI findings may be secondary to the limited number of available fMRI studies or to heterogeneity across paradigms employed (Fusar-Poli et al., 2008).

Additionally, we could not address the question how consistent brain changes are at specific times in particular anatomical regions. Overall, neuroimaging studies of people who later develop psychosis comprised small samples and might therefore not

be representative. Some studies used standard VBM, while others used an 'optimized' VBM method (Good et al., 2001). However, the use of VBM or optimized VBM method implicates compatibility problems (Ashburner and Friston, 2000). The size of the smoothing kernel is also relevant, because it should be roughly the size of the expected findings. In addition, gray matter reductions may also reflect a variety of neuropathological changes, e.g. exaggerated dendritic or synaptic pruning (McGlashan and Hoffman, 2000)), impaired myelination (Bartzokis et al., 2003), apoptosis (Glantz et al., 2006), or neurotoxic effects of antipsychotic medications (Reinke et al., 2004). Furthermore, differences in scanning parameters, image analysis and packages may account for inconsistencies in neuroimaging measures (Fusar-Poli et al., 2008).

Together with the concept of early detection of psychosis, the time point of therapeutic intervention was pushed back before the onset of frank psychosis (McGorry et al., 2009). A clinical staging model suggests safer, more benign intervention in early high-risk state and could help to design randomised control trials without confounders such as antipsychotic medication. Although brain structural and functional abnormalities were evident in antipsychotic-naïve HR subjects (Hurlemann et al., 2008; Job et al., 2005; Koutsouleris et al., 2009b; Pantelis et al., 2003; Thompson et al., 2007; Whalley et al., 2006), antipsychotic medication may also contribute to progressive brain structural and functional alterations observed in studies including HR subjects after they have developed psychosis (Smieskova et al., 2009). It is an intrinsic difficulty in longitudinal studies of HR subjects, as once a subject has developed frank psychosis, immediate treatment with antipsychotic medication is indicated. An alternative approach is to conduct follow up scanning before the onset

of psychosis, while subjects are usually antipsychotic-naïve. This may reveal longitudinal changes that predate the onset of illness and that are not confounded by the effects of antipsychotic medication. Overall, longitudinal imaging studies may have the advantage of powerful, within-subject designs, while multi-site studies may overcome the problem of small sample sizes and bridge basic neuroscience with clinical psychiatry.

5. CONCLUSIONS

Despite a wide range of methodological differences between studies, structural and neurochemical abnormalities in prefrontal, anterior cingulate and medial temporal cortex might be predictive for a development of psychosis. Neuroimaging studies of high-risk patients who later develop psychosis may in future lead to neuroanatomical and neurofunctional markers. These markers could be initially used in a multi-domain early detection approach and at a later stage enable the prediction of disease transition at an individual level. Although clinical relevance of brain abnormalities in this group is not completely established yet, neuroimaging studies in prodromal putative subjects could provide the targets for early intervention that could potentially prevent a chronic clinical trajectory of the illness.

Acknowledgements

This study was supported by grants from the Swiss National Science Foundation (Project No. 3232BO_119382).

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TABLE AND FIGURE LEGENDS

TABLE 1: Selection criteria employed to define clinical high-risk groups

TABLE 2: Neuroimaging studies included in the review

TABLE 3: Structural imaging studies of individuals at high-risk of psychosis

TABLE 4: Meta-analysis of structural findings

TABLE 5: Neurofunctional imaging studies of individuals at high-risk of psychosis

TABLE 6: Meta-analysis of functional findings

FIGURE 1: Flowchart of the studies considered and included according to the design