Brain structural and neurofunctional correlates of liability to psychosis

A multimodal neuroimaging approach

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Preface

The work described in this thesis was conducted from June 2008 until Mai 2011 under the guidance of Prof. Dr. Stefan Borgwardt and Prof. Dr. Jürgen Drewe at the Department of Biomedicine, University Hospital Basel.

Part of this thesis has already been published in or submitted to peer reviewed journals. These manuscripts are included in the respective paragraphs. References in these sections are independent from the rest of this PhD thesis.

Pages in the thesis are numbered consequently. There are two separate page numbers in already published manuscripts. The page numbers appearing bottom rights are relevant for the thesis.

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Abbreviations used in the thesis

ANCOVA - analysis of covariance
ANOVA - analysis of variance
ARMS 'at-risk mental state'
ARMS-LT - long-term ARMS
ARMS-NT - ARMS with no transition to psychosis
ARMS-ST - short-term ARMS
ARMS-T - ARMS with transition
BSIP - Basel Screening Instrument for Psychosis
BPM - Biological Parametric Mapping
BPRS - Brief Psychiatric Rating Scale
BOLD - Blood-oxygen-level-dependent
CBT - Cognitive behavioral therapy
CSF - Cerebro-spinal fluid
DARTEL - Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra
DSM-IV - Diagnosis and Statistical Manual of Mental Disorder IV
FEPSY - *Früherkennung von Psychosen* - Early Detection of Psychosis Clinic
FE - First episode of psychosis
FWE - Family-wise error
EPI - Echo planar sequence
fMRI – Functional magnetic resonance imaging
GMV – Gray matter volume
GABA – Gamma aminobutyric acid
GAF - Global Assessment of Functioning
MNI – Montreal Neurological Institute
MPRAGE – Magnetization prepared rapid gradient echo
MRI - Magnetic resonance imaging
PACE - Personal Assessment and Crisis Evaluation Clinic, Melbourne
PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SANS - Scale for the Assessment of Negative Symptoms
SPM8 – Statistical parametric mapping
SPSS - Statistical Package for Social Sciences
sMRI – Structural magnetic resonance imaging
VBM8 – Voxel-based morphometry
WM - Working memory
XBAMM – Brain activation and morphological mapping

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Chapter 1

INTRODUCTION

Schizophrenia is a complex multifactorial chronic and disabling mental disorder affecting one of hundred people worldwide. It is a syndrome of signs and symptoms of unknown etiology, predominantly defined by signs of psychosis (Insel 2010). Psychosis is commonly considered as a rare phenomenon outside the range of normal experience giving rise to significant disability (Dominguez, et al. 2011).

The history of this mental illness goes back thousands of years from the mental symptoms resembling schizophrenia as signs of heart diseases in the ancient Egypt and the evil possession of the body in middle ages. Its modern history dates to Emil Kraepelin who defined schizophrenia as premature dementia in young adults in the late nineteenth century (Kraepelin 1919). At the beginning of the twentieth century, Eugen Bleuler introduced the term 'schizophrenia' and described four 'A' disturbances: associations, affect, ambivalence, and autistic isolation (Bleuler 1920). Kurt Schneider emphasized psychotic symptoms as delusions and hallucinations and narrowed the definition of schizophrenia (Schneider 1959). The DSM-IV (Diagnosis and Statistical Manual of Mental Disorder-IV) definition synthesizes abovementioned signs: a Kraepelinian emphasis on course, Schneiderian positive psychotic symptoms and Bleuler's reconceptualized negative symptoms (Andreasen and Black 2001). Nowadays the characterization as a neurodevelopmental disease is accepted (Pantelis, et al. 2003b). It is postulated, that a set of basic biological abnormalities that occur early in life leads to a combination of structural, functional, and/or biochemical anomalies in the developing brain (Cannon, et al. 1993). Currently two neuronal disruption pathways are assumed: pruning-related plasticity process during adolescence (Bartzokis, et al. 2003) and stress-related neurotoxic effects (Hof, et al. 2003).

Psychosis nearly always emerges in late adolescence or early adulthood. It means in a period of life characterized already in healthy typically developing individuals by rapid changes in biological, cognitive, and emotional development. Global gray matter starts to decrease gradually and global white matter continues to increase in healthy subjects (Sowell, et al. 1999). This process seems to be impaired in people prone to psychosis.

Characteristic features of psychosis are impaired insight into the pathological nature of experienced delusions or hallucinations (Lysaker, et al. 2007; Mohamed, et al. 2009; Palaniyappan, et al. 2010), as well as cognitive and functional alterations. Along with the 'positive' symptoms such as hallucinations, ego-disturbances and delusions, the typical loss of functioning accompanied with lack of energy and social withdrawal belong to the 'negative' symptoms.

The underlying pathophysiology of schizophrenia is not entirely understood (Thompson, et al. 2009) but involves dysregulation in several neurotransmitter systems in the brain. A previously postulated hyperdopaminergic hypothesis based on the antagonistic effect of antipsychotics on D2-receptors has been changed. There is neither single abundance nor single deficiency of dopamine in the psychotic brains (Carlsson 1988). Along with this dopamine dysregulation, serotonin, Gamma aminobutyric acid

(GABA) and glutamate (Carlsson 2006) may induce both the positive and the negative symptoms of schizophrenia and contribute to cognitive deficits and functional decline.

1.1 Pharmacological treatment of psychosis

Despite decades of research and advances in interventions, schizophrenia continues to be one of the most severe psychiatric disorders. The pharmacological intervention has been changing parallel to the growing understanding of neurobiological basis of schizophrenia. During the 1950's and 1960's, the typical antipsychotics revolutionized its treatment. The typical antipsychotics (such as chlorpromazine, haloperidol, loxapine, molindone, perphenazine, sulpiride and thioridazine) were primarily referred as first generation or conventional antipsychotics. Their antagonistic mode of action on the D2-receptors (Carlsson 1978; Seeman, et al. 1975) leads mainly to the reduction of positive symptoms. The typical antipsychotics have no effect on negative and cognitive symptoms and could cause side effects such as extra-pyramidal symptoms, sedation, and prolactin elevation (Stahl 2008).

Atypical antipsychotics – also known as second generation antipsychotics - (for example olanzapine, risperidone, quetiapine, clozapine, ziprasidone and aripiprazole) showed highly specific pharmacological properties depending on their unique receptor profiles. Although the atypical antipsychotics offered better tolerability (substantially lower risk of extrapyramidal symptoms), there were still cardio-metabolic side effects and weight gain occurring (Lieberman, et al. 2008) and no significantly better effect on functional recovery and cognitive deficits compared to typical antipsychotics (Keefe, et al. 2007). Recent animal and human studies have shown that both typical and atypical antipsychotic agents may cause alterations of regional gray matter volumes (Dazzan, et al. 2005; Konopaske, et al. 2008; Navari and Dazzan 2009) that were not solely attributable to disease-related effects.

1.2 The prodromal stage of schizophrenia

The prodromal stages of serious physical diseases, e.g. cardiovascular and oncological diseases, have become more attention recently. Similarly, over the last decades early clinical detection and intervention in patients with psychoses has become widespread. Psychosis seems to be preventable or at least successfully treatable in the early stages (McGorry, et al. 2007). Early detection services worldwide (Mechelli, et al. 2010; Riecher-Rössler, et al. 2009; Yung, et al. 1998) identify individuals, who are experiencing prodromal symptoms characterized by attenuated psychotic symptoms and a decline in social and occupational function and broadly termed as having a clinical high-risk or at risk mental state (for review see (Riecher-Rössler, et al. 2006)). Research in early and prodromal phases of the illness may provide important etiology findings that are not confounded by medication and/or chronic disease related effects.

The developing psychosis is understood as a continuum with early mild clinical signs. A high-risk state of psychosis may be a consequence of a genetic predisposition (Lawrie, et al. 2008) and/or gene-

neurodevelopmental interaction (Borgwardt, et al. 2007b; DeLisi 2008; Pantelis, et al. 2005) and/or other stress factors leading to the increased clinical risk for psychosis. Around 20-30% (Riecher-Rössler, et al. 2007; Riecher-Rössler, et al. 2009; Yung, et al. 1998) of these high-risk individuals go on to develop psychosis with more severe symptoms and some of them continue to a serious chronic disease. Research has attempted to identify definitive markers that distinguish those, who go on to develop psychosis from those, who do not. However, it is difficult to identify the individuals, who will later develop psychosis on clinical or symptomatic grounds. Therefore, we are facing the need to characterize vulnerability- and resilience-associated neurobiological markers. Neuroimaging methods help to clarify the mechanisms underlying psychosis, as the same individuals can be studied before and after the onset of illness, often with only minimal confounding effects of the previous treatment.

The term 'at-risk mental state' (ARMS) has been suggested as a replacement of the term 'prodromal', to delineate a subthreshold syndrome that confers high – but not inevitable – risk for development of psychotic disorder in the near future (Yung, et al. 1998). The ARMS is defined according to the PACE (Personal Assessment and Crisis Evaluation Clinic, Melbourne) criteria and requires individuals to present attenuated positive psychotic or brief limited intermittent symptoms that do not reach full psychosis threshold (Riecher-Rössler, et al. 2007; Riecher-Rössler, et al. 2009; Yung, et al. 2004) or functional decline. These psychopathological symptoms are often associated with negative symptoms (Lencz, et al. 2004; Riecher-Rössler, et al. 2009), subtle cognitive deficits (Brewer, et al. 2006; Riecher-Rössler, et al. 2009) and include deficits in cognitive domains (Broome, et al. 2010; Simon, et al. 2007). Furthermore, neurofunctional deficits may be associated with transition to psychosis and thus can be seen as vulnerability markers for developing schizophrenia (Morey, et al. 2005; Riecher-Rössler, et al. 2009).

1.3 Transition to psychosis and resilience factors

Importantly, most of the ARMS individuals who made transition (90.5%) did so in the first two years after their ARMS was ascertained (ARMS with transition, ARMS-T). After these two years, only 3% of included ARMS individuals developed psychosis {Riecher-Rössler, 2009, Efficacy of using cognitive status in predicting psychosis: a 7-year follow-up}. In a study by Yung, the vast majority of transitions occurred in the first two years (estimated hazard ratio 0.58) and significantly dropped over time (estimated hazard ratio 0.07) (Yung, et al. 2007).

Some recent studies aiming to improve individual risk assessment also report, that transition rate was declining over time (Haroun, et al. 2006; Ruhrmann, et al. 2010). During first two years, the transition rate declined from 31% published in 2003 (Pantelis, et al. 2003a) to 16% published five years later in the high-risk population (Yung, et al. 2008). This decline could be the result of non-pharmacological interventions, such as psychosocial intervention, family support, cognitive behavioral therapy (CBT) or other unknown (possibly protective) factors.

Some ARMS individuals may have better internal resources, attitudinal approaches and overall functioning as seen by unmedicated schizophrenia patients (Harrow and Jobe 2007). They may recover

subsequently (Simon and Umbricht 2010). Other individuals may be on the ARMS continuum for a longer period of time. The more the subclinical psychosis persist in general population over time, the greater the risk of transition to clinical psychosis as showed an 8–year study (Dominguez, et al. 2011). Those ARMS individuals, who are more vulnerable to transition, can have less resilient factors and vice versa. That is the reason, why we suggest splitting the individuals in at-risk mental state according to the duration of their ARMS as well as according to their outcome (Figure 1). The first criterion focuses on the time aspect of risk: the short-term ARMS (ARMS-ST) group are ARMS individuals for a period of two years starting the first day of their ARMS; to the second group (long-term ARMS, ARMS-LT) belong individuals, who are in ARMS continuum longer than two years. ARMS-LT individuals represent a group with a vulnerability to psychosis but a reduced transition probability (Riecher-Rössler, et al. 2009). It is essential, that all of the ARMS (ARMS-ST and ARMS-LT) still meet the PACE criteria and no individuals who recovered are included. ARMS-ST subjects are vulnerable to psychosis and 20-40% out of them will transit (ARMS-T) in next two years, leaving still 60-80% of ARMS without transition to psychosis - ARMS-NT (ARMS with no transition to psychosis). Actually those ARMS-NT, who did not recover and still fulfill ARMS criteria are of high importance and should be called ARMS-LT. We should follow them with the aim to investigate resilience factors protecting them in the process of on-going psychosis.

Thus the two ARMS subgroups (ARMS-ST and ARMS-LT) represent vulnerability to psychosis with different probabilities of later transition to psychosis. ARMS-LT group is clearly on the risk continuum to develop psychosis, but according to the published data has lower probability to develop subsequent psychosis than ARMS-ST. This interesting group could help us to define resilient factors in at risk mental state.

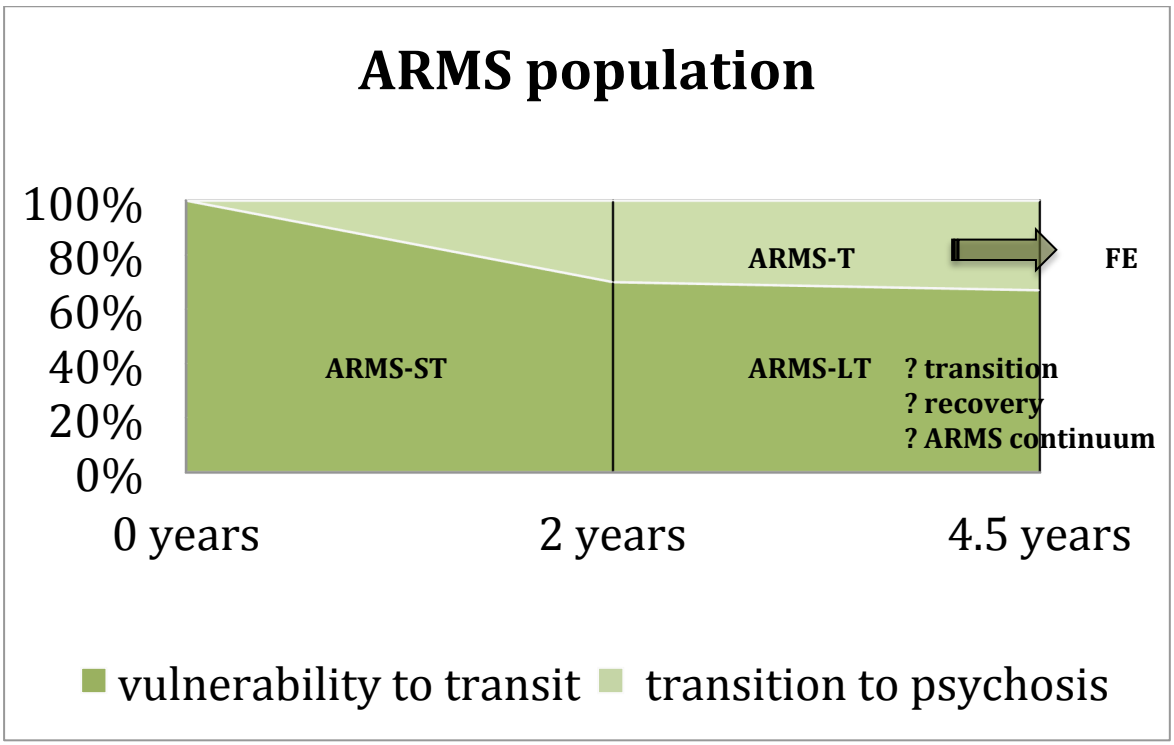

Figure 1: **ARMS population vulnerable to psychosis with descending transition probability in a time course of their at-risk state**.

ARMS individuals can be divided according to the duration of their at-risk mental state into ARMS-ST (ARMS short-term) and ARMS-LT (ARMS long-term) individuals. ARMS individuals with subsequent transition to psychosis (ARMS-T) can continue to develop first episode of psychosis (FE). ARMS-LT can be followed-up clinically and investigated for their vulnerability- and resilience-associated factors.

1.4 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) techniques permits the examination of brain structure (sMRI) and function (fMRI) *in vivo*. MRI is a non-invasive method, safe scanning procedure without necessity to use ionizing radiation or injection of chemical substances. MRI scanner uses a strong magnetic field and radio transmitter and creates 2D or 3D image slices. Image resolution of sMRI images allows differentiating between gray (neurons and neuropil), white (myelinated fiber connections between neurons) matter tissue and cerebro-spinal fluid (CSF). By using the paramagnetic properties of oxygenated and deoxygenated hemoglobin and measuring the blood-oxygen-level-dependent (BOLD) contrast, regional cerebral blood flow and resulting 'brain activity' during cognitive task (McGuire, et al. 2008) can be compared across groups.

1.4.1 Structural brain imaging findings in ARMS

Over the past decade, sMRI methods have been extensively employed to identify the anatomical alterations in the pre-psychotic phases. Several techniques were implemented to investigate structural differences in ARMS individuals: voxel-based morphometry for gray matter (Borgwardt, et al. 2007a; Koutsouleris, et al. 2009; Pantelis, et al. 2003b) and white matter (Walterfang, et al. 2008), region-of-interest approach (Fornito, et al. 2008; Phillips, et al. 2002; Takahashi, et al. 2009a; Thompson, et al. 2007; Velakoulis, et al. 2006; Wood, et al. 2005; Yucel, et al. 2003), cortical pattern matching (Sun, et al. 2009; Takahashi, et al. 2009b), and gyrification index (Harris, et al. 2007). In subjects at high-risk for psychosis with subsequent transition to psychosis, as compared to the high-risk individuals without subsequent transition, MRI studies showed volumetric reductions in frontal, insular, cingulate, lateral and middle temporal, and cerebellar regions (Borgwardt, et al. 2007a; Borgwardt, et al. 2008; Borgwardt, et al. 2007b; Fornito, et al. 2008; Koutsouleris, et al. 2009; Pantelis, et al. 2003a; Pantelis, et al. 2003b; Sun, et al. 2009; Takahashi, et al. 2009a; Takahashi, et al. 2009b).

These regions are compatible with the regions of structural deficits found in first-episode schizophrenia (Kasai, et al. 2003; Lieberman, et al. 2001; Steen, et al. 2006; Vita, et al. 2006; Witthaus, et al. 2008) and in the relatives of schizophrenic patients (Borgwardt, et al. 2010; Goghari, et al. 2007). The latter indicates that volumetric reductions in these regions represent potential vulnerability markers for psychosis.

1.4.2 Neuropsychological findings in ARMS

Executive function impairments including working memory (WM) (Callicott, et al. 2003a; Cannon, et al. 2005; Forbes, et al. 2009; Glahn, et al. 2005; Jansma, et al. 2004; Johnson, et al. 2006; Manoach, et al. 2000; Menon, et al. 2001; Schneider, et al. 2007), spatial memory and verbal fluency deficits (Becker, et al. 2010; Frommann, et al. 2010; Fusar-Poli, et al. 2010b; Hambrecht, et al. 2002; Korver, et al. 2010;

Ozgurdal, et al. 2009; Pauly, et al. 2010; Seidman, et al. 2010), and reward and salience processing anomalies (Juckel, et al. 2006; Murray, et al. 2008; Roiser, et al. 2009; Simon, et al. 2010) are pronounced cognitive features found in schizophrenia. However, the relation of physiological and clinical variables (positive, negative symptoms) is complicated by the multidimensional nature of psychotic symptoms. Recent advances in psychiatric research indicate that neurocognitive deficits are also evident in subjects with an at-risk mental state (ARMS) (Eastvold, et al. 2007; Marjoram, et al. 2006; Pflueger, et al. 2007; Simon, et al. 2007; Smith, et al. 2006) and in non-affected first-degree relatives (Karch, et al. 2009; Karlsgodt, et al. 2007; Lee, et al. 2010a; MacDonald, et al. 2009; Meda, et al. 2008; Spence, et al. 2000).

1.4.3 Functional brain imaging findings in ARMS

The fMRI studies are based on the known impaired cognitive domains in the early stages of schizophrenia. They use an 'activation paradigm', which engages the brain region/s of interest and the results reflect abnormalities under these specific cognitive domains. Some of the published fMRI studies investigated neurofunctional abnormalities in ARMS and found deficits in the frontal and temporal task-related networks (Allen, et al. 2010; Fusar-Poli, et al. 2007a). Several studies focused on functional deficits, while performing a working memory task (Broome, et al. 2010; Broome, et al. 2009; Fusar-Poli, et al. 2010c; Fusar-Poli, et al. 2010d). Such alterations cannot be attributed to the effects of illness or treatment and may represent markers of vulnerability to psychosis (Fusar-Poli, et al. 2007a).

Chapter 2

GENERAL OUTLINE AND AIMS OF THE THESIS

Post-mortem and neuroimaging studies of schizophrenic or psychotic patients showed less gray matter volumes and larger ventricles than brains of healthy people (Wright, et al. 2000). Although the majority of the included patients had history of antipsychotic treatment, the effect of antipsychotics on the brain structure received previously little attention. Apart from that, drug treatment might induce detectable changes in the brain of treated individuals (Dazzan, et al. 2005). This was the reason, why we firstly reviewed the effect of antipsychotics on the brain structure of schizophrenic patients treated with different antipsychotics. Our results are described and discussed in the **chapter 4.1**. We also contributed to the growing discussion in this clinically relevant issue with our two letters to the editors and with a commentary to recently published paper.

Beside of the effect of antipsychotics there are also other possible confounders in studies with psychotic individuals, such as duration of their psychotic symptoms, comorbidity with other symptoms, medication with antidepressants and substance abuse. That is why the other aim of my thesis, addressed in the **chapter 4.2**, was to analyze the neuroimaging predictors of transition to psychosis. We focused on a population of high-risk individuals who are mostly not medicated yet and are at the beginning of their disease. In our meta-analysis we have evaluated the differences between those ARMS individuals who later developed psychosis and those, who did not.

Initial theoretical analyses were followed by analyses of structural and functional neuroimaging data. We investigated individuals vulnerable to psychosis and those with the first episode of schizophrenia. Different probability for subsequent transition to psychosis was characterized according to the duration of the at risk mental state. We were interested in volumetric abnormalities in antipsychotic naïve high-risk individuals, as described in **chapter 4.3.** Additionally, we evaluated the association between volumetric abnormalities and clinical measures.

Neurofunctional activation in a working memory task was evaluated together with gray matter volume as regressor in each voxel. This multimodal approach enables us to characterize the regions where functional abnormalities can be associated with volumetric deficits. Characterization of vulnerability- and psychosis-related neurofunctional differences in a working memory network was the main aim of the study in **chapter 4.4**.

Chapter 3

METHODS AND MATERIALS

The detailed information about used methods and materials belongs to each manuscript of already published or submitted publication. These manuscripts are included in the respective paragraphs. All used methods are briefly described underneath.

In the **chapter 4.1,** we performed a comprehensive electronic search on publications studying schizophrenia patients treated with antipsychotic medication. We presented a number of quantitate measures in informative tables and provided interpretation of the neuroimaging findings. We have focused on the antipsychotic medication, especially its type and doses, calculated chlorpromazine equivalents, and we characterized affected brain regions.

Chapter 4.2 provides systematic review according to the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) guidelines (Moher, et al. 2009). We have calculated the effect sizes with an estimator corrected for the number of subjects included in each study, using Cohen's d statistic (Cohen 1992). Mean effect sizes were calculated for the most consistent results across the studies, i.e. for global brain volume measurements.

Chapter 4.3 and **4.4** are based on specific population of individuals in the high risk to develop psychosis. Those were compared with first episode of psychosis patients and with matched healthy controls.

Since 1999, the Early Detection of Psychosis Clinic (*Früherkennung von Psychosen* - FEPSY) in Basel recruited and followed up the ARMS individuals up to 7 years (Borgwardt, et al. 2007a; Riecher-Rössler, et al. 2007; Riecher-Rössler, et al. 2009). Subjects were assessed using the 'Basel Screening Instrument for Psychosis' (BSIP) (Riecher-Rössler, et al. 2008; Riecher-Rössler, et al. 2007), the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Negative Symptoms (SANS) and the Global Assessment of Functioning (GAF). The BSIP evaluates 'prodromal' symptoms (defined according to the Diagnosis and Statistical Manual of Mental Disorder, DSM-III-R) occurring in the last 5 years; nonspecific 'prodromal' signs (Riecher-Rössler, et al. 2007) in the last 2 years; previous or current psychotic symptoms, psychosocial functioning over the last 5 years, substance dependency; and psychotic disorders among first and second degree relatives (Riecher-Rössler, et al. 2008).

ARMS individuals were identified, examined, treated and followed-up at regular intervals: during the first year of follow-up once monthly, during the second and third year every 3 months, and thereafter annually (Riecher-Rössler, et al. 2009). Transition to psychosis was monitored according to the transition criteria (Yung, et al. 1998). We analyzed clinical and socio-demographic data using one-way analysis of variance (ANOVA) with the Statistical Package for Social Sciences (SPSS 16.0 and SPSS 19.0)

In the **chapter 4.3**, we used T1-weighted MPRAGE sequences on a 3T scanner (Siemens Magnetom Verio, Siemens Healthcare, Erlangen, Germany) and examined the acquired images using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm; Wellcome Department of Cognitive Neurology, London, United Kingdom). We preprocessed the images using voxel-based morphometry - VBM8 toolbox

(http://dbm.neuro.uni-jena.de/vbm8/) with integrated New Segmentation and DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra) approaches. Our segmented, normalized and smoothed images were entered into the statistical analysis of covariance (ANCOVA). The statistical model comprised age, gender, and total gray matter volume as covariates of no interest.

Using the same scanner and echo planar (EPI) sequences we acquired fMRI images elicited with an n-back (working memory) task (**chapter 4.4**). The reaction times and response accuracy were recorded on-line. After exclusion of error trials, we convolved the onset times for each trial in seconds with a canonical hemodynamic response function. Firstly, we evaluated and described functional and structural data separately. The second important step was an integrative image analysis of two imaging data sets – fMRI data as the primary modality and structural VBM data as corresponding covariate. We used Biological Parametric Mapping (BPM) (Casanova, et al. 2007b) toolbox to provide this multimodal analyses with two imaging and three non-imaging covariates.

Statistical inferences in our analyses were made at $p<0.05$ after family-wise error (FWE) correction and the regions of brain activation labeled in MNI coordinates were transformed into Talairach space (www.ebire.org/hcnlab/cortical-mapping; Talairach Daemon software).

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The Effects of Antipsychotics on the Brain: What Have We Learnt from Structural Imaging of Schizophrenia? – A Systematic Review

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Abstract: Despite a large number of neuroimaging studies in schizophrenia reporting subtle brain abnormalities, we do not know to what extent such abnormalities reflect the effects of antipsychotic treatment on brain structure. We therefore systematically reviewed cross-sectional and follow-up structural brain imaging studies of patients with schizophrenia treated with antipsychotics. 30 magnetic resonance imaging (MRI) studies were identified, 24 of them being longitudinal and six cross-sectional structural imaging studies. In patients with schizophrenia treated with antipsychotics, reduced gray matter volume was described, particularly in the frontal and temporal lobes. Structural neuroimaging studies indicate that treatment with typical as well as atypical antipsychotics may affect regional gray matter (GM) volume. In particular, typical antipsychotics led to increased gray matter volume of the basal ganglia, while atypical antipsychotics reversed this effect after switching. Atypical antipsychotics, however, seem to have no effect on basal ganglia structure.

Key Words: Schizophrenia, antipsychotics, typical, atypical neuroleptics, conventional, MRI, neuroimaging.

1. INTRODUCTION

Schizophrenia is a severe psychiatric disorder that affects about 1% of the population and is one of the top ten causes of disability worldwide [1]. Despite decades of research the neurobiological basis of schizophrenia is still largely unknown [2]. However, modern neuroimaging techniques have enabled us to examine the brains of patients with schizophrenia *in vivo*. A large body of neuroimaging studies have reported that as the illness proceeds, patients rapidly lose cerebral gray matter (GM), particularly in the frontal, temporal and limbic lobes [3, 4]. The treatment of schizophrenia involves the use of antipsychotic drugs (typical antipsychotics, such as haloperidol), which act as antagonists at central dopamine D_2 receptors [5, 6], although some of them have additional effects on other receptors [7]. A new generation of antipsychotic drugs, the atypical antipsychotics (for example quetiapine, olanzapine, risperidone and clozapine), with a lower affinity and occupancy for the dopaminergic receptors, but an additional occupancy for the serotoninergic 5-HT_{2A} and other receptors [8] have become available. Antipsychotics are effective in reducing the severity of positive psychotic symptoms but have limited impact on negative symptoms, cognitive impairment and produce a range of side effects including extra-pyramidal symptoms, prolactin elevation, sedation and cardio-metabolic effects [7]. Compared to typical antipsychotics, atypical antipsychotics induce less extra-pyramidal adverse effects and more metabolic adverse effects [7] but the underlying neurobiological mechanisms are still unclear.

One way to better understand these mechanisms is to use neuroimaging to investigate structural brain changes associated with a specific class of antipsychotic drugs. Neuroimaging is a potentially powerful tool to explore the impact of antipsychotic medication on brain structure in schizophrenia. Neuroimaging studies indicate that schizophrenia is associated with neuroanatomical abnormalities, with robust evidence of reduced GM volume in a number of cerebral regions [9, 10]. In particular these studies demonstrated volumetric reductions in the whole brain, in the prefrontal cortex and in the superior and medial temporal lobes [4, 11-14]. These neuroimaging findings are also supported by post-mortem studies [15, 16].

Studies of schizophrenia and other psychiatric disorders have suggested that the ability of antipsychotic medication to induce anatomical and molecular changes in the brain may be relevant for its antipsychotic properties in addition to their action on neurotransmission [17-21]. However, despite considerable research, a major concern for neuroimaging studies of patients with schizophrenia is the potential confound of antipsychotic medication. Thus, it remains unclear to what extent structural changes are due to the ongoing illness process and to what extent to medication and how different antipsychotic medications affect neuroimaging measures. The aim of this article is to systematically review neuroimaging studies addressing the impact of antipsychotic medication on brain structure. In addition, we examine the different effects of typical and atypical antipsychotic medication.

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2. METHODS

Selection Procedures

Search Strategy

Electronic searches were performed using PUBMED database on antipsychotic medication and neuroimaging. Since our main focus was to examine potential different medication effects of typical and atypical antipsychotics on neuroimaging measures, we included all existing structural neuroimaging studies of adult and childhood-onset schizophrenia published until November 2008, without any language restriction. Patients met diagnostic criteria for schizophrenia or schizophreniform or schizoaffective disorder according to Diagnostic and Statistical Manual of Mental Disorders DSM-III-R or DSM-IV criteria. The search terms were: schizophrenia, antipsychotic medication, typical antipsychotic, atypical antipsychotic, conventional antipsychotic, basal ganglia, ventricular enlargement, caudate, cortical gray, white matter (WM), morphometry, brain imaging, neuroimaging, magnetic resonance imaging, and MRI.

Selection Criteria

First, studies that investigated brain structure and differences between groups of patients treated with typical or atypical antipsychotics were included. We hand-searched all the publications in order to find longitudinal and cross-sectional neuroimaging studies considering the effects of antipsychotic medication as well as the references of all manuscripts for further relevant publications. To qualify for inclusion in this review the studies must have: (a) been an original publication in a peer-reviewed journal (b) studying schizophrenic patients using neuroimaging techniques according to antipsychotic medication (c) considering the differences in medication either among various antipsychotic medications or over the time among various groups of patients.

According to their clinical stage, patients with schizophrenia were considered as patients with a first episode (defined as first hospitalization [22], less than five years` total duration of disease [23]), recent onset (first hospitalization within the last 5 years [22]), chronic patients (disease duration greater than five years [24], disease duration more than ten years [23]), or therapy resistant chronic patients (chronic and refractory to conventional treatment [25]). We used the term antipsychotic-naïve for those patients who have never used any antipsychotic medication and 'antipsychotic-free' for patients free of antipsychotic medication for at least two months before admission [26].

Recorded Variables

One approach for systematic reviews is to survey the literature and then provide an informed interpretation of the main findings. However, with this approach the review's summarising process may be opaque to the reader, who cannot assess the validity of the conclusions without reading the original papers. In the present review we have tried to help the readers to form their own opinion by presenting a number of key quantitative measures from the studies reviewed in informative tables. Two of the authors extracted the data independently (SB and RS). The recorded variables for articles used in the review were: type of medication, mean dose of the used drugs, chlorpromazine equivalents, regional volumetric brain differences, type of study design (longitudinal/cross-sectional) and imaging analysis method (region-of-interest, voxel-based morphometry) and the demographic characteristics of patients groups.

3. RESULTS

In recent years a large number of neuroimaging studies have been conducted to evaluate the variations and longitudinal changes in brain structure in various groups of patients, often reporting contradictory results. 30 studies published between 1996 and 2008 met the inclusion criteria and were reviewed, 24 of them being longitudinal and six cross-sectional structural imaging studies. Table **1** contains an overview of all reviewed studies for better orientation.

Structural Neuroimaging Studies

We reviewed structural MRI studies evaluating GM volume differences between patients and healthy controls (cross-sectional) as well as progressive changes (longitudinal) in whole and regional brain volumes and compared these between groups of patients according to their antipsychotic treatment.

Cross-Sectional MRI Studies

In total, six cross-sectional MRI studies were reviewed. Two cross-sectional studies compared patients treated with typical antipsychotics only to healthy controls [22, 24] and four studies compared patients treated with different antipsychotics [3, 23, 27].

The results of Kopelman *et al.* suggest that patients treated with typical antipsychotics have a thicker cortical depth of the left anterior cingulate gyrus without displaying any difference in surface area compared to healthy controls [24]. In another study increasing exposure to typical antipsychotics correlated with a larger insular volume, but the differences between patients and healthy controls were not significant [22].

Brain structural changes associated with the use of typical or atypical antipsychotics in first-episode psychosis patients are mostly qualitative, because they appear as significant in each group compared only to the drug-free group. Treatment with typical antipsychotics was associated with an enlargement of the basal ganglia and size reductions in insula, extending into inferior frontal and superior temporal gyrus, in lobulus paracentralis, anterior cingulate gyrus and precuneus [27]. However, treatment with atypical antipsychotics was associated solely with an enlargement of the thalami [27]. Pituitary volume was 30 % larger in the first-episode patients receiving typical antipsychotics and 17% larger in patients receiving atypical antipsychotics compared to healthy controls [28]. Higher doses of a typical antipsychotic were associated with larger caudate, putamen and thalamus volumes, whereas a higher dose of an atypical antipsychotic only with larger thalamic volume [3]. First-episode schizophrenic patients treated with atypical antipsychotics had larger hippocampal volumes than those treated with typical antipsychotics [23]. The specifics of each of these cross-sectional MRI studies have been included in Table **2**.

Table 1. Overview of Reviewed Studies

Study (Reference)	Population				Specification of Study Design	Medication	CPZ E mg/d	Medication	CPZ E mg/d
		Patients				Typicals, n of Subjects, Mean Dose		Atypicals, n of Subjects, Mean Dose	
	C	Typical	Atypical	AF/AN					
Chakos *et al.* - 2004 [42]	10	8 FE		21 AN	standardized neuroleptic regimens fewer than 12 weeks or none (enter of the study)	up to 3 diff. neuroleptics (n of subjects n/a)	400 - 900	up to 3 diff. neuroleptics (n of subjects n/a)	400 - 900
Chakos *et al.* - 2005 [23]	26	22 (17 FE, 5 ChP)	32 (15 FE, 17 ChP)	–	FE: 17 haloperidol, 15 atypicals = 12 olanzapine, 3 risperidone, 1 clozapine+molindone, 1 unknown; Ch P: 5 typicals = 3 haloperidol, 1 trifluoroperzine, 1 thiothixene,17 atypicals = 6 olanzapine, 8 clozapine, 3 risperidone	17 haloperidol, 1 clozapine+molindone, Ch P: 5 typicals = 3 haloperidol, 1 trifluoroperzine, 1 thiothixene	n/a	12 olanzapine, 3 risperidone, 1 clozapine+molindone; 6 olanzapine, 8 clozapine, 3 risperidone	n/a
Christensen *et al.* - 2004 [30]	8	16 FE		–	AF baseline → 4 week continued hospitalization: 4 mg risperidone, 7 mg haloperidol, 120 mg ziprasidone	haloperidol (7 mg)	350	risperidone (4 mg), ziprasidone (120 mg)	200; 200
Chua *et al.* - 2008 [31]	–	15 FE	5 FE	25 AN	–	13 haloperidol, 1 trifluorperazine, 1 sulpirid	318	5 amisulpirid	318
Corson *et al.* - 1999 [46]	–	13 FE (5 typ + atyp.)	10 FE (4 type + typ.)	–	time of intake: 4 AN, 14 typ., 5 typ.+ atyp.;	haloperidol, trifluoperazine, thiothixene, fluphenazine, thioridazine, perphenazine, chlorpromazine (n of subjects n/a)	n/a	clozapine, risperidone, olanzapine (n of subjects n/a)	n/a
Dazzan *et al.* - 2005 [27]	–	32 FE	30 FE	13 AN + 9 AF	cross-sectional non-randomized, VBM	chlorpromazine, sulpiride, haloperidol, thioridazine, droperidol, trifluoperazine, zuclopenthixol (n of subjects n/a)	269.5±245	21 olanzapine (14mg), 5 risperidone (4mg), 2 quetiapine (400mg), 1 sertindole (16mg), 1 amisulpiride (400mg)	280; 200; 533; sertindole n/a; 400
Frazier *et al.* - 1996 [38]	8	–	8	–	2 years	1 haloperidol (1mg/d)	50	8 clozapine (400 mg/d)	800
Garver *et al.* - 2005 [26]	7	6 (3 FE)	13 (7 FE)	–	scan before and after 28 days of treatment	6 haloperidol (7mg/d)	350	7 risperidone (4mg/d) and 6 ziprasidone (120mg/d);	200 and 200
Girgis *et al.* - 2006 [35]	15	–	15 AN	–	6 week follow-up	–	–	15 risperidone 2,67±1.23mg	133
Gogtay *et al.* - 2004 [37]	38	–	23 COS	–	baseline: 22 medication (17 typ. and 5 atyp.) → follow up 23 atyp.:during study most recived atyp.	baseline 17 typ. (n of subjects n/a)	–	baseline: 5 atyp., folow-up: 23 atyp. (15 clozapine)	n/a
Gur *et al.* - 1998 [3]	128	48 PT ChP - only typ.	27 PT ChP typ. + atyp.	21 AN	–	48 typ. (28 haloperidol, 8 haloperidol dekanoat, 6 loxapine, 8 thioridazine, 3 molindone, 12 thiothixene, 4 fluphenazine, 4 fluphenazine decanoat, 9 trifluoperazine, 7 perphenazine, 8 chlorpromazine), 22 typ. + atyp. (15 clozapine, 16 risperidone)	407.1	22 typ. + atyp. (15 clozapine, 16 risperidone), 5 only risperidone	58.2 - 3723.5; 150-400; 286.3

(Table 1) contd….

Study (Reference)	Population				Specification of Study Design	Medication	CPZ E mg/d	Medication	CPZ E mg/d
		Patients				Typicals, n of Subjects, Mean Dose		Atypicals, n of Subjects, Mean Dose	
	C	Typical	Atypical	AF/AN					
Heitmiller *et al.*- 2004 [43]	14		14 AN FE		only atyp.	–	–	7 males: 2 risperidone, 1 olanzapine later quetiapine, 3 risperidone and/or olanzapine, 1 risperidone olanzapine finally clozapine; 7 females: 2 risperidone, 1 risperidone and /or quetiapine, 1 olanzapine, 3 risperidone and/or olanzapine	n/a
Ho *et al.* - 2003 [49]	23	40 RO	–	33AN	naturalistic study	7 typ., 11 typ. + atyp.	462.2	20 atyp. (olanzapine, quetiapine, risperidone, ziprasidone), 15 clozapine	462.2
James *et al.* - 2004 [39]	16	–	16 COS	–	–	–	–	16 atyp., 3 also clozapine	279
Kopelman *et al.*- 2005 [24]	30	30 (6 FE, 11 RO, 13 ChP)	–	–	only males	only typicals (n of subjects n/a)	CPZ equvalents from 0.5 to 650 "dose-year"	–	–
Lang *et al.*- 2004 [44]	23	10 ChP	37	–	baseline typ. (10) or risperidone (13) - limited response switched to olanzapine, 14 patients receiving risperidone - good response - continued	baseline (10): loxapine, trifluoperazine, chlorpromazine, fluphenazine, haloperidol switched to olanzapine	360.1	baseline: 13 risperidone switched to olanzapine, 14 patients receiving risperidone - good response - continued	olanzapine switched from typicals 170.0 + switched from risperidone 150.0; risperidone 84.0
Lieberman *et al.*- 2005 [32]	58	82 FE	82 FE	–	double blind randomized week 0, 12, 24, 52, 104	82 haloperidol (2-20mg/d)	100-1000	82 olanzapine (5-20mg/d)	100-400
Massana *et al.* - 2005 [36]	–	–	11 AN	–	baseline: AN → 3 months risperidone	–	–	14 risperidone, mean dose 6.05mg/d	302.5
McClure *et al.*- 2006 [29]	–	2 stabile ChP	6 stabile ChP	–	2 scans within 4-8 weeks 8 ChP stable treatment	1 thiothixene (10mg/d), 2 perphenazine (8mg/d)	200; 800	1 clozapine (800mg/d), 1 quetiapine (200mg/d) + risperiodne (4mg/d), 1 olanzapine (30mg/d), 1 olanzapine (5mg/d), 1 olanzapine (20mg/d), 1 risperiodne (9mg/d) + quetiapine (400mg/d)	1600; 267; 200; 600;100; 400; 450; 533.3
McClure *et al.* 2008 [33]	–	–	10 ChP	–	off medication 39.4 days, then brief period (12 weeks) atypicals	–	–	olanzapine (10-20mg/day); risperidone (4-6mg/day); quetiapine (300-800mg/day); clozapine (500-1000mg/day) (n of subjects n/a)	200-400; 200-300;400-1067;1000-2000
McCormick *et al.* 2005 [48]	18	9 AN	22 AN	–	–	5 haloperidol, 2 perphenazine, 1 fluphenazine, 1 thiothixene (8 pure, 1 mixed)	dose years	10 risperidone, 11 olanzapine, 1 clozapine (15 pure, 7 mixed)	dose years

(Table 1) contd….

Study (Reference)	Population				Specification of Study Design	Medication	CPZ E mg/d	Medication	CPZ E mg/d
		Patients				Typicals, n of Subjects, Mean Dose		Atypicals,n of Subjects, Mean Dose	
	C	Typical	Atypical	AF/AN					
Molina *et al.*- 2005 [25]	11	–	12 ChP TR	17 AN	AN: risperidone 5 ± 2mg/d, ChP TR: baseline – haloperidol 10 mg/d 1 month → converted to clozapine initial 410 ± 339 mg/d, final 260 ± 211 mg/d	–	–	risperidone (5 ± 2mg/d), clozapine (260 ± 211 mg/d) (n of subjects n/a)	100 ± 40; 520 ± 422
Pariante *et al.* - 2005 [28]	78	33 FE	26 FE	12 AN + 6 AF	cross-sectional non-randomized, ROI	3 depot, others oral	n/a	19 olanzapine, 5 risperidone, 1 sertindole, 1 amisulprid	n/a
Pressler *et al.*- 2005 [22]	30	30 (6 FE, 11 RO, 13 ChP)	–	–	typ. at the time of scanning	only typicals (n of subjects n/a)	CPZ equvalents from 0.5 to 650 "dose-year"	–	–
Scheepers *et al.* - 2001 [45]	–	–	26 ChP	–	baseline scan before discontinuating typ., after 24 weeks follow-up	baseline: 26 patients typ.	527	follow up: 26 patients clozapine (mean dose 345.57mg/d)	691.1
Stip *et al.* - 2008 [34] Letter to the Editor	–	1 ChP	15 ChP	–	baseline: haloperidol, risperidone, olanzapine → 2 week discontinuation → 20 weeks quetiapine	1 haloperidol (10mg)	500	9 risperidone (3.3 ±1.4m0), 6 olanzapine (21.2±6.29mg) → 2 week discontinuation → 20 weeks quetiapine (529mg)	165; 424; 705.3
Strungas *et al.*- 2003 [47]	5	–	7 (3 FE, 4 ChP)	–	min 2 months of medication non-compliance → drug-free period of psychosis exacerbation → 4 mg risperiodone	–	–	7 risperidone 4mg	200
Tauscher-Wisniewski *et al.* - 2002 [41]	–	4 FE	9 FE	8	baseline: 8 AN, 7 FE - mean lifetime antipsychotic exposure in chlorpromazine equivalents 15.1; → 4 month: 4 typ. + 9 atyp. + 2 typ and atyp.	2 haloperidol (2mg/d), 2 loxapine (10 mg/d)	–	4 olanzapine (14.4mg/d), 2 risperidone (2.5mg/d), 3 clozapine (333mg/d); 2 typ+ atyp.: clozapine (400mg/d)	288; 125; 666; 800
Tauscher-Wisniewski *et al.* - 2005 [40]	37	–	10 AN	–	subgroup of 10 patients 2 scans at 12 weeks	–	–	10 quetiapine 494mg	660
Thompson *et al.* - 2008 [2]	–	15 FE	21 FE		double blind treatment	15 haloperidol 5mg/d	250	21 olanzapine 10mg/d	200

All studies are also referenced in the text. Abbreviations C = control; AN = antipsychotic-naïve; AF = antipsychotic free; PT = previously treated; FE = first episode; RO = recent onset; TR = treatment resistant; ChP = chronic patient; BG = basal ganglia; CPZ = chlorpromazine; CPZ E = chlorpromazine equivalent; VBM = voxel-based morphometry; ROI = region of interest; BT = before therapy; AT = after therapy; GM = gray matter.

Longitudinal MRI Studies Using Voxel-Based Morphometry (VBM)

In total, 13 longitudinal MRI studies using VBM methods were reviewed. Two studies of patients treated with typical and atypical antipsychotics did not examine the differences between subgroups of antipsychotic medication [29, 30]. Another four longitudinal studies searched for progressive changes after treatment with either of atypical antipsychotics [2, 26, 31, 32]. Seven studies evaluated the changes in brain structure after medication with only atypical antipsychotic medication [33-39]. Three studies assessed chronic patients with schizophrenia [29, 33, 34], two studies focused on childhood-onset psychosis [38, 39], whereas the other studies only included patients with first-episode schizophrenia [2, 26, 30-32, 35-37]. The brain changes were compared with a healthy control group comprising healthy volunteers in seven studies [26, 30, 32, 35, 37-39].

A study that examined the effects of medication with typical antipsychotics revealed GM increases in basal ganglia volume [32], whereas the basal ganglia volume remained unchanged following treatment with atypical antipsychotics [34].

Table 2. Cross-Sectional MRI Studies of Patients with Schizophrenia

Study (Reference)	Medication	Population				Regional differences in GM			Regional differences in GM			Regional Differences in GM		
			Patients											
		C	Typical	Atypical	AF/ AN	Typical vs drug-free	Voxels	x y z	Atypical vs drug-free	Voxels	x y z	Typ. vs Atyp.	Voxels	x y z
Chakos *et al.* - 2005 (23)	atyp. + typ.	26	22 (17 FE, 5 ChP)	32 (15 FE, 17 ChP)	–	–	–	–	–	–	–	FE treated with atyp. higher hippocampal volume than FE treated with haloperidol - males treated with atypicals early in illness lose less hippocampal volume	–	–
Dazzan *et al.* - 2005 (27)	atyp. + typ.	–	32 FE	30 FE	13 AN + 9 AF	↑ in R lenticular nucleus	563	23.1 -3.1 2.6	↑ in L and R thalamus	310	-2.9 -25.8 4.8	↓ in L middle TG (BA 21)	196	-53 -14.6 -10.4
						↓ in 1) R insula, extending into inferior FG (BA 47), superior TG (BA 22)	741	37 12.3 -4.6	–	–	–	–	–	–
						↓ in 2) L and R paracentral lobule (BA 4,5), extending into superior and medial FG (BA 6, 31), CG (BA 24)	717	0 -22.2 46.7	–	–	–	–	–	–
						deficits in 3) L precuneus	472	-1.3 -47.4 49.4	–	–	–	–	–	–
Gur *et al.* - 1998 (3)	typ. and typ. + atyp., atyp.	128	48 PT ChP - only typ.	27 PT ChP typ. + atyp.	21 AN	higher dose of typicals associated with higher caudate, putamen, thalamus volumes	–	–	higher dose of atypicals associated with higher thalamus volume	–	–	–	–	–
Kopelman *et al.* - 2005 (24)	only typ., only males	30	30 (6 FE, 11 RO, 13 ChP)	–	–	↑ of L ACG vs C due to ↑ in cortical depth without any difference in surface area	–	–	–	–	–	–	–	–
Pariante *et al.* - 2005 (28)	atyp. + typ.	78	33 FE	26 FE	12 AN + 6 AF	pituitary volume 30% larger vs controls	–	–	pituitary volume 17% larger vs controls + 15% larger by antipsy-chotic free vs controls	–	–	pituitary volume of patients receiving typicals is showing trend to be 11% larger vs other groups of patients (p=0.08)	–	–
Pressler *et al.* - 2005 (22)	typ.	30	30 (6 FE, 11 RO, 13 ChP)	–	–	nonsign. ↑ volume of insular cortex in medicated vs Cs - increasing exposure to typ. (in dose-years) correlated with larger insular volume	–	–	–	–	–	–	–	–

All studies are also referenced in the text. Abbreviations x y z = Talairach coordinates; C = control; AN = antipsychotic naïve; AF = antipsychotic free; PT = previously treated; FE = first episode; RO = recent onset; TR = chronic resistant; ChP = chronic patient; BG = basal ganglia; ↑ = excess, increase, higher; ↓ = decrease, deficit; R = right; L = left; TG = temporal gyrus; FG = frontal gyrus; CG = cingulate gyrus; BA = Brodmann area; typ. = typical antipsychotics; atyp. = atypical antipsychotics

The study by Lieberman *et al.* [32] is the only controlled, double blind, randomized, multi-site longitudinal study. With a relatively large sample size of seventy-nine patients with first-episode schizophrenia, patients treated with haloperidol showed significant reductions in GM volume compared to healthy controls. In contrast, olanzapine-treated patients did not show any significant decreases in GM volume during the follow up period. GM reduction in the haloperidol group was evident during the first 12 weeks in frontal GM and at week 52 in the temporal and parietal GM. Significant volume increases in the caudate nucleus in the haloperidol group were observed at weeks 24, 52 and 104 compared to olanzapine group [32].

In another study by Thompson *et al.* the dynamics of illness progression in treated patients were shown for typical versus atypical antipsychotic drugs [2]. The haloperidol-treated group showed the fastest tissue loss in the frontal cortex during the first year of psychosis. In the olanzapine group the brain changes occurred more posteriorly in occipital and limbic regions. These results suggest that antipsychotic medication may not be entirely protective. The volumetric changes related to antipsychotic medication are regionally much more pronounced than it would be predicted from healthy controls. However, the differences between the medication groups were less pronounced after a 12-month period [2].

Among a small sample of patients with chronic schizophrenia, relative volume increases in left hippocampal GM were found in patients treated with atypical, but not with typical antipsychotics [29]. Patients treated with typical antipsychotics showed a trend towards decreasing total cerebrospinal fluid (CSF) volume [29]. In medication-free chronic patients treated briefly with atypical antipsychotics no significant changes in GM volume were observed [33]. Results from another study of patients with chronic schizophrenia showed greater GM density in the basal ganglia after 20 weeks of medication with quetiapine [34]. These findings were contradictory to previous short-term follow up studies [26, 29, 33].

Individuals with first-episode psychosis, who received short-term treatment (six weeks) with risperidone, showed increased GM volume in the temporal cortex and decreased GM in frontal cortex. Risperidone-treatment was associated with reduced WM and was found in the corpus callosum, cerebellum and right anterior cingulate [35].

In childhood-onset schizophrenia clozapine treated patients had larger caudate volume compared to healthy controls [38]. However, after two years of clozapine treatment, caudate volume did not differ between baseline and follow-up scan [38]. In adolescent-onset schizophrenia, smaller volumes in the prefrontal cortex and thalamus, a larger fourth ventricle volume and a reduced cerebellar (i.e. vermis) volume were found in a longitudinal study with patients treated with atypical antipsychotics [39].

Relative to antipsychotic-naïve patients, patients receiving treatment (15 with typical, five with atypical antipsychotics) had relatively greater GM volumes in the caudate and in the cingulate gyri extending to the left medial frontal gyrus [31] after three-four weeks of treatment. Results from recently decompensated antipsychotic-free schizophrenic patients showed no evidence, that a four-week antipsychotic treatment itself may cause volumetric change in cerebral WM volume [30]. Patients with childhood-onset schizophrenia treated for two years with atypical antipsychotics showed GM reductions in parietal and fronto-temporal cortices as well as reduced total GM volume [37]. The specifics of each of these longitudinal VBM studies have been included in Table **3**.

Longitudinal Studies Using a Region-of-Interest (ROI) Approach

In total, 11 longitudinal MRI studies using ROI methods were reviewed. Seven longitudinal studies using an ROI approach focused on basal ganglia [40-46], one on the thalamus [47], one on the anterior cingulate gyrus [48] and two studies on other cortical regions [25, 49]. Five studies evaluated GM changes after treatment with atypical antipsychotic medication only [25, 40, 43, 45, 47], four compared typical versus atypical antipsychotic [41, 44, 46, 48] and two did not examine for the differences between these two subtypes of antipsychotic drugs [42, 49].

No differences between baseline and follow-up in caudate volumes were seen in a subgroup of ten patients after 12 weeks of quetiapine treatment [40]. After a five-year follow-up only an age-related decline in caudate volume in patients' treatment with both typical and atypical antipsychotics and healthy controls was found [41]. At the beginning the antipsychotic-naïve patients treated exclusively with atypical antipsychotics showed only a negligible volume enlargement of the caudate after two years, but these changes may be sex-dependent [43]. Female patients with a greater amount of drug exposure had fewer enlargements of caudate nuclei. In males the correlation was reversed [43]. Treatment with typical antipsychotics was associated with larger basal ganglia volumes and switching to olanzapine was associated with a reduction in basal ganglia volumes [44]. Volumes of putamen and globus pallidus were normalized following the switch to olanzapine. In the group of risperidone-treated patients, who later switched to olanzapine, no significant differences in overall basal ganglia volume were seen [44]. Treatment with clozapine in schizophrenic patients previously treated with typical antipsychotics resulted in decreased caudate volume [45]. Volume of caudate and nucleus lentiformis increased after exposure to typical antipsychotics and decreased following exposure to atypical antipsychotics [46]. Caudate volumes increased in first-episode patients during 18-month treatment by 5.7% and decreased by 1.6% in healthy controls [42].

Several other longitudinal studies in chronic and first episode treated with both typical and atypical medication have produced evidence for GM volume changes in different regions including the parietal and occipital lobes [25] and thalamic volume [49]. Exposure to typical antipsychotics was associated with an increase in anterior cingulate cortex (ACC) volume over time while exposure to the atypical class of antipsychotics was associated with a decrease in volume of ACC over time [48]. Progressive brain changes in patients with schizophrenia occur despite ongoing antipsychotic drug-treatment, however, no significant differences were

Table 3. Longitudinal MRI Studies of Patients with Schizophrenia

Specification	Study (Reference)	Medi-cation	Population				Regional Differences in GM			Regional Differences in GM			Regional Differ-ences in GM
			C	Patients									
				Typical	Atypical	AF/AN	Typical vs Drug-Free	Num. of Voxels	x y z	Atypical vs Drug-Free	Num. of Voxels	x y z	Typical vs Atypical
VBM / whole brain	Christensen *et al.* – 2004 [30]	typ. + atyp	8	16		–	responders of treatment (13 patients - ↓ of SAPS) - ↓ of WMV, 3 drug-nonresponders – nonsign. ↑ of WMV; no evidence, that antipsychotic treatment itself caused volumetric change in cerebral WMV					–	–
	Chua *et al.* – 2008 [31]	typ. + atyp	–	15 FE	5 FE	25 AN	typ.+atyp. vs AN after 3-4 weeks: GMV excess in 1) L CG extending to L medial FC,L caudate nucleus (9%) (BA 0, BA 24)	593	-0.6 21.8 5.1	–	–	–	–
			–	–	–	–	2) R CG extending to R caudate nucleus (10%) (BA 0, BA 24)	93	4.9 21.2 2.4	–	–	–	–
	Frazier *et al.* – 1996 [38]	atyp.	8	–	8	–	–	–	–	baseline: caudate ↑ in COS vs C, 2years → no diff. between 2 groups, non-sign. ↓ putamen volume in COS vs C, non-sign. ↑ of lateral ventricles in COS vs C	–	–	–
	Garver *et al.* – 2005 (26)	typ. + atyp	7	6 (3 FE)	13 (7 FE)	–	no effect	–	–	↑ of cortical gray volume, ↓ of CSF and WM volumes, no effects on the basal ganglia	–	–	cerebral cortical gray expanded, no effects on the basal ganglia
	Girgis *et al.* – 2006 [35]	atyp.	15	–	15 AN	–	–	–	–	between baseline and follow-up ↑ GM: 1) L superior TG (BA39) 2) L middle TG (BA39) and ↓ GM 3) LFG, rectal gyrus (BA11) ↓ WM 4) L cerebrum, subjacent to FG 5) L corpus callosum 6) R cerebrum, subjacent to FG, 7) R corpus callosum 8) R AC		1) -45,-59,19 2) -57,-54,14 3) -2,43,-26 4) -19,22,17 and -16,16,21 5)-10,23,15 6)23,19,18 7)15,17,21 8)7,28,15	–
	Gogtay *et al.* – 2004 [37]	atyp.	38	–	23	–	–	–	–	–	–	–	longitudinally less P, F, T, total GMV
	James *et al.* – 2004 [39]	atyp.	16	–	16 COS	–	–	–	–	patients (all medicated) had ↓ mean volume in the prefrontal cortex ($p<0.001$) and thalamus ($p=0.04$) vs C; larger volumes of the fourth ventricle ($p=0.05$); longitudinally only evidence of progression in posterior inferior vermis volume amonge males			–

(Table 3) contd….

Specification	Study (Reference)	Medi-cation	Population				Regional Differences in GM			Regional Differences in GM			Regional Differences in GM
			C	Patients									
				Typical	Atypical	AF/AN	Typical vs Drug-Free	Num. of Voxels	x y z	Atypical vs Drug-Free	Num. of Voxels	x y z	Typical vs Atypical
	Lieberman *et al.* – 2005 [32]	typ. + atyp	58	79FE	82 FE	_	haloperidol group - ↓ of WBGM (frontal, temporal, parietal) over time, most during the first 12 weeks, ↑ in lateral ventricle and caudate	_	_	olanzapine group – retained WBGM	_	_	caudate volumes ↑ in haloperidol group vs olanzapine, magnitude of differences between groups was constant over time, but significance was lost
	Massana *et al.* – 2005 [36]	atyp.	_	_	11 AN	_	_	_	_	↑ in GM volume L and R caudate and L accumbens	_	_	_
	McClure *et al.* – 2006 [29]	typ. + atyp	_	2 ChP	6 ChP	_	_	_	_	_	_	_	↑ in left hippocampal volume in atypic vs typ; trend towards ↓ total CSF volume in typ.
	McClure *et al.* – 2008 [33]	atyp.	_	_	10 ChP	_	_	_	_	no longit. change in R or L caudate, GMV, no effect of treatment status in F or T GMV, in WMV, in CSF volume in 3nd , 4th or lateral ventricles and in cortical sulci	_	_	_
	Stip *et al.* – 2008 [34]	atyp.	_	1	15 ChP	_	↑ GMd in BG before treatment with quetiapine: 1) L caudate 2) R caudate nucleus 3) R putamen 4) L putamen	1) 4551 2) 506 and 638 3) 20 4) 64	1)-14,20,6 2)18,2,19 and 12,17,0 3) 34,2,2 4) 31,0,5	↑ GMd in BG after treatment with quetiapine: 1) L pallidum 2) R putamen	1) 1402 2) 530 and 124	1) -22,-6,0 2) 31,-22,4 and 27,14,12	_
	Thompson *et al.* – 2008 [2]	typ. + atyp	_	15 FE	21 FE	_	Trajectory of GM deficits:lateral parietal-temporal (3 month) → dorsolateral, medial frontal and prefrontal (6 months)→ most of the FC (1 year). Medial wall: 1. posterior CC → anteriorly → limbic cortex (6 months) → F and preF C (12 months); 2. posteriorly → occipital C. FC = greatest deficits – intense in 6 and 12 months			changes more posteriorly – occipital and limbic regions – changes are much higher than would be predicted to occur normally			typical-treated vs atypical-treated: greater GM deficits in medial and superior C (3 and 6 months) → only frontal cortex (12 months) – not signifi-cant after stringent multiple comparisons correction
ROI	Chakos *et al.* – 2004 [42]	typ. + atyp	10	8 FE		21 AN	caudate volumes increased in FE during 18-month treatment by 5,7% (greater by patients before medicated or younger) and de-creased by HC 1.6%	_	_	_	_	_	_

(Table 3) contd….

Specification	Study (Reference)	Medication	Population				Regional Differences in GM			Regional Differences in GM			Regional Differences in GM
			C	Patients									
				Typical	Atypical	AF/AN	Typical vs Drug-Free	Num. of Voxels	x y z	Atypical vs Drug-Free	Num. of Voxels	x y z	Typical vs Atypical
	Corson *et al.* – 1999 [46]	typ. + atyp	–	13 FE (5 typ + atyp.)	10 FE (4 atyp + typ.)	–	typ.: ↑ volume of caudate and lentiform nucleus	–	–	atyp.: ↓ volume of caudate and lentiform nucleus	–	–	–
	Heitmiller *et al.*- 2004 [43]	atyp.	14	–	14 AN FE	–	–	–	–	negligible ↑ in volume of the caudate over 2 years; females – the greater amount of drug exposure, the less enlargement , males – opposite – the greater the enlargement of caudate	–	–	–
	Ho *et al.* – 2003 [49]	typ. + atyp	23	73 (33 AN, 40 RO)		–	no significant effects from 4 treatment (typ.; atyp.; typ.+ atyp.; clozapine) measures on any ROIs – progressive volumetric brain changes despite antipsychotic treatment						–
	Lang *et al.* – 2004 [44]	typ. + atyp	23	10 ChP	37 (13 switched from risperidone, 14 continued)	–	baseline: typ. – BG greater (putamen by 7%, globus pallidus 20.7%) vs contols → switch to olanzapine: putamen volume ↓ by 9.8% + globus pallidus by 10.7% - did not differ from controls	–	–	risperidone-treated switched → olanzapine: no significant differences in overall BG	–	–	switch to olanzapine: putamen volume ↓ by 9.8% + globus pallidus by 10.7% → did not differ from controls
	McCormick *et al.* – 2005 [48]	typ. + atyp	18	9 AN	22 AN	–	increased typical exposure → increased ACC over time	–	–	increased atypical exposure → decreased ACC over time	–	–	the mean change in ACC volume – very small with large standard deviations
	Molina *et al.* – 2005 [25]	atyp.	11	–	12 ChP TR	17 AN	baseline: ChP TR typ., than atyp.	–	–	AN baseline: ↑ in O GM + P GM vs C, ↓ in total + O WM vs C; longitudinally: the greater the initial deficit in total and P GM, the greater the increase in GM + the greater the initial excess total WM and its change in total and O WM, the greater the longitudinal decreases; ChP TR : ↑ in total, F GM, P and O GM vs C + ↓ in total, F, P, O WM vs C; longitudinally: the greater the baseline volume excess of WM, the greater the ↓ in total, F, P and O WM			
	Scheepers *et al.* – 2001 [45]	atyp.	–	–	26 (typ. before)	–	–	–	–	–	–	–	clozapine ↓ in CNV after typ. treatment; no difference in CNV changes between responders and non-responders, no changes in total brain volume
	Strungas *et al.* – 2003 [47]	atyp.	5	–	7 (3 FE, 4 ChP)	–	–	–	–	drug-free period: patients – trend smaller thalamic volumes ($p<0.06$); 4 weeks of treatment: volumetric expansion of L and R thalamus	–	–	–

(Table 3) contd….

Specification	Study (Reference)	Medi-cation	Population				Regional Differences in GM			Regional Differences in GM			Regional Differences in GM
			C	Patients									
				Typical	Atypical	AF/AN	Typical vs Drug-Free	Num. of Voxels	x y z	Atypical vs Drug-Free	Num. of Voxels	x y z	Typical vs Atypical
	Tauscher-Wisniewski *et al.* - 2002 [41]	typ. + atyp	–	4	9	8	–	–	–	age-related ↓ in CNV 9% between baseline and follow-up in FE as well as C	–	–	–
	Tauscher-Wisniewski *et al.* - 2005 [40]	atyp.	37	–	10 AN	–	–	–	–	no difference between baseline and endpoint in CNV	–	–	–

All studies are also referenced in the text. Abbreviations x,y,z = Talairach coordinates (MNI coordinates uncounted by www.bioimagesuite.org/Mni2Tal/index.html); C = control; AN = antipsychotic naïve; AF = antipsychotic free; PT = previously treated; FE = first episode; RO = recent onset; TR = chronic resistant; ChP = chronic patient; BG = basal ganglia; ↑ = excess, increase, higher; ↓ = decrease, deficit; R = right; L = left; TG = temporal gyrus; FG = frontal gyrus; CG = cingulate gyrus; BA = Brodmann area; typ. = typical antipsychotics; atyp. = atypical antipsychotics; GMV = gray matter volume, GMd = gray matter density; WM V= white matter volume; WBGM = whole brain gray matter; FC = frontal cortex; CC = cingulate cortex; ACC = anterior cingulate cortex; CSF = cerebrospinal fluid; COS = childhood onset schizophrenia; typ. = typicals; atyp. = atypicals; SAPS = Schedule for assessment of positive symptoms; FGM = frontal gray matter; OGM = occipital GM; PGM = parietal GM; DLFG = dorsolateral frontal gyrus; SMA = supplementary motor area; CNV = caudate nuclei volume

seen among the four different treatment groups (typical antipsychotics, atypical antipsychotics, typical + atypical antipsychotics, clozapine) [49]. The specifics of each of these longitudinal ROI studies have been included in Table **3**.

4. DISCUSSION

Structural neuroimaging studies can be used to examine the influence of antipsychotics on brain structure. Overall, structural imaging studies suggest that medication with typical antipsychotics leads to an increased volume of the basal ganglia, while atypical antipsychotics reduce this volume after switching.

Effects of Antipsychotic Medication on Structural Neuroimaging Measures in Schizophrenia

There is a convergence of findings from structural neuroimaging studies described showing volumetric reductions in fronto-temporo-limbic regions may reflect pathophysiologic processes of schizophrenia [9, 12]. Studies of patients with schizophrenia demonstrate robust volumetric reductions in multiple brain regions and particularly in the prefrontal cortex and of the superior and medial temporal lobes and in the anterior cingulate [4, 11-14].

While these findings are consistent and replicated, there are inconsistencies regarding the potential effect of antipsychotic medication. Some studies found no significant effect of antipsychotic medication on brain structure [30, 33, 40, 41, 49]. However, in many of these studies, the sample sizes were modest (< 30 subjects) resulting in type 2 errors. Other studies found ameliorative effects of (mostly atypical) antipsychotics on structural neuroimaging measures [38, 44, 50, 51]. Generally, both typical and atypical antipsychotics respectively the illness process itself were associated with GM volume reductions in occipital and limbic regions [2].

In general, functional imaging studies underline findings from structural neuroimaging studies. They suggest that treatment with atypical antipsychotics has been associated with greater regional cortical activity compared to treatment with typical antipsychotic drugs, whereas the latter have been associated with relatively more striatal activity [52]. Atypical antipsychotics (substitution of risperidone for typical antipsychotic) also increased prefrontal activity (prefrontal cortex, supplementary motor area) during cognitive tasks (working memory) and reduced abnormally elevated subcortical limbic activity during emotion processing so that brain activity resembled that observed in healthy volunteers [50]. These findings might reflect pathophysiologic processes that may be at least partly ameliorated by antipsychotic medication. Clozapine but not haloperidol treatment re-established normal task-activated regional cerebral blood flow (CBF) patterns in schizophrenia in the ACC [53]. This is consistent with the finding that atypical antipsychotics might have a greater effect on cognitive impairment in schizophrenia than typical [54].

Progressive brain changes in schizophrenia are considered controversial [55]. Although there is evidence for GM loss and ventricular enlargement from prospective studies of patients with first episode and chronic schizophrenia [49, 56-61], the potential confounding impact of antipsychotics is still debatable. Most neuroimaging studies of schizophrenia to date have not included the examination of non-medicated patients, making conclusions about medication effects on

neuroimaging measures difficult. Investigation of subjects at the onset of the disease avoids potential confounders such as antipsychotic treatment [62-65]. A clinical high-risk status for psychosis (at risk mental state, ARMS) is associated with a set of neurofunctional abnormalities that are qualitatively similar to those observed in patients with the disorder [66]. As these findings are not attributable to chronic psychotic symptoms [67] and antipsychotic treatment, they may represent markers of increased vulnerability to psychotic disorders. Structural MRI studies of non-medicated patients in a prodromal phase of psychosis or ARMS demonstrated that neuroanatomical abnormalities are already evident in the very early phase of psychosis. People at high risk of psychosis show qualitatively similar volumetric abnormalities to patients with schizophrenia. Cortical brain abnormalities have been found in genetically defined high-risk populations such as first-degree relatives and co-twins of patients with schizophrenia, as well in people with ARMS [13, 68-80]. Previous longitudinal MRI studies in this group found that the subset of patients who developed psychosis showed a longitudinal reduction in GM in the orbito-frontal, temporal lobe, parietal lobe and cerebellum [79, 81, 82].

Mechanisms of Antipsychotic Action on Brain Structure

At present, the mechanism of action of antipsychotics is inferred from animal and *in vitro* studies. Structural neuroimaging has contributed substantially to the understanding of the mechanisms of action of existing antipsychotic drugs. Thompson *et al.* [2] suggest pharmacologic mechanisms that go beyond symptom suppression *via* neuroreceptor antagonism. Those mechanisms might ameliorate the underlying pathophysiology that causes disease progression and the clinical deterioration that is the hallmark of the illness [2].

Furthermore, it has been suggested that antipsychotics might increase neurogenesis, however, neurogenesis seems contradictory to studies showing that antipsychotics are associated with volume reductions. Haloperidol treatment may be neurotoxic [25, 83] which may explain the cortical GM volume reduction. In a very recent study, Konopaske *et al.* [84] found a significant 20.5% reduction in astrocyte numbers and a non-significant 12.9% reduction in oligodendrocytes in antipsychotic-exposed macaque monkeys. Similar effects were seen in both haloperidol and olanzapine treated patients. These very intriguing findings of antipsychotic-induced glial cell number reduction in animals, however, need to be replicated. In humans, treated with typical antipsychotics, frontal GM volume reduction is correlated with the dose [3]. Medication-free subjects with an ARMS show fronto-temporal tissue reduction relative to healthy controls [79, 81, 82], suggesting that the loss process is not attributable solely to medication.

Atypical antipsychotics reduce oxidative stress [85] and stimulate the synthesis of trophic molecules [85-88]. In primates, treatment with atypical antipsychotics led to prefrontal glial cell proliferation and cortical hypertrophy [89]. In rats, olanzapine stimulates glial cell division in the frontal cortex [85]. Thus, atypical antipsychotics may reduce disturbed myelination and abnormally severe dendritic pruning and/or neurotoxic ablation of synapses [49, 90, 91] in patients with schizophrenia. Atypical antipsychotics may also induce oligodendrocyte proliferation and compensate for oligodendrocyte reductions [49] and intracortical myelination [90].

Methodological Issues in Studies Investigating Medication Effects by Neuroimaging

Some studies used VBM, a technique that allows comparisons of the entire brain volume at the single voxel level. Mostly, an 'optimized' VBM method [92] is used to minimize the potentially confounding effects of errors in stereotactic normalization was used. It is important to note that to identify regional differences in GM volume instead of GM concentration, 'modulated' versions of VBM, which involves the multiplication of the spatially normalized GM by its relative volume before and after warping, were used. However, the use of VBM implicates problems of brain registration [93]. The size of the smoothing kernel is also relevant, because it should be roughly the size of the expected findings. Although the exact meaning of the volumetric abnormalities is not entirely clear, GM reductions may reflect a variety of neuropathological changes, e.g. exaggerated dendritic or synaptic pruning [94], impaired myelination [90], apoptosis [95], or other neurotoxic effects of first-generation antipsychotic medications [96]. Furthermore, differences in scanning parameters and image analysis may account for inconsistencies in neuroimaging measures.

The results of this review raise ethical questions on antipsychotic use. If antipsychotic medication may lead – at least in some patients - to GM volume reduction careful benefit-risk decisions have to be made for individual patients. Patients with schizophrenia should be very cautiously informed about the potential risks (and of course benefits) of antipsychotic medication.

For future studies, we suggest to focus on, longitudinal designs that represent the gold standard for investigation of medication effects. These studies have clearly the advantage of powerful, within-subject designs. Small sample sizes, heterogeneity in the sociodemographic characteristics of the subjects, lack of consistency between scanning parameters also suggest future multi-site studies that have shown the potential to overcome most of these problems and to bridge basic neuroscience with clinical psychiatry.

5. CONCLUSIONS

In patients with schizophrenia treated with antipsychotics, reduced GM volume is described, particularly in frontal and temporal lobes. Medication with typical antipsychotics also leads to increased volume of the basal ganglia, while atypical antipsychotics reversed the effect after switching.

Neuroimaging studies have provided compelling evidence that despite antipsychotic medication (both typical and atypical) there are detectable anatomical changes at the level of total and regional brain volumes. To date, it remains elusive whether the effects of antipsychotic medication on GM volume are simply beneficial. It is questionable whether the effects we are observing are the direct effects of antipsychotics or whether these measures are actually surrogates for third variables. It is also possible that the opposite could be true, that antipsychotics may attenuate the brain changes and

that compliance with medication could lead to less progressive change than non-compliance. Unless we do not have more reliable studies from non-medicated patients, the potential impact of the confounding effect of medication has to be kept in mind. So far, the investigation of patients at risk or with a first-episode of schizophrenia seems to be the most promising alternative.

CONFLICT OF INTEREST

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ABBREVIATIONS

ACC = Anterior cingulate cortex

ARMS = At risk mental state

CBF = Cerebral blood flow

CSF = Cerebrospinal fluid

DSM = Diagnostic and statistic manual of mental disorders

GM = Gray matter

MRI = Magnetic resonance imaging

ROI = Region-of-interest

VBM = Voxel-based morphometry

WM = White matter

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COMMENTARY

The effects of antipsychotics on brain structure: what have we learnt from structural imaging of schizophrenia?

A commentary on 'Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings' by Navari & Dazzan (2009)

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Key words: Antipsychotics, ARMS, brain structure, MRI, schizophrenia.

Introduction

We read with great interest the article by Navari & Dazzan (2009) recently published in *Psychological Medicine*. These authors found that antipsychotic treatment may contribute to brain structural changes observed in psychosis and that antipsychotics act regionally rather than globally on the brain, with specific effects on different brain structures.

In an own systematic review on the effects of antipsychotics on the brain (Smieskova *et al*. in press) we summarized findings from structural imaging studies of schizophrenia. We focused on studies investigating schizophrenia patients using neuroimaging techniques according to antipsychotic medication and studies considering the differences in medication either in various antipsychotic medications or over the time or in various groups of patients. Overall, we found that patients with schizophrenia receiving treatment with antipsychotics had reduced grey matter (GM) volume, particularly in frontal and temporal lobes. Medication with typical antipsychotics also leads to increased volume of the basal ganglia, while atypical antipsychotics reversed the effect after switching. Studies with typical antipsychotics have reported increased GM volume in cingulate cortex, in contrast to atypical antipsychotics with the excess more often seen in thalamus volume.

Confounding effects of antipsychotics

As discussed by Navari & Dazzan (2009), the potential confounding impact of antipsychotics on progressive brain changes in schizophrenia is considered controversial (DeLisi, 2008). Although there is evidence for GM loss and ventricular enlargement from prospective studies of patients with first-episode and chronic schizophrenia (Wood *et al*. 2008), most neuroimaging studies of schizophrenia to date have not included the examination of non-medicated patients, making conclusions about medication effects on neuroimaging measures difficult. Investigation of subjects at the onset of the disease avoids potential confounders such as antipsychotic treatment (Riecher-Rossler *et al*. 2007). A clinical high-risk status for psychosis (at-risk mental state, ARMS) is associated with a set of neurofunctional abnormalities that are qualitatively similar to those observed in patients with the disorder (Fusar-Poli *et al*. 2007). As these findings are not attributable to chronic psychotic symptoms or antipsychotic treatment, they may solely represent markers of increased vulnerability to psychotic disorders. Cross-sectional structural MRI studies of non-medicated patients in a prodromal phase of psychosis or ARMS demonstrated that neuroanatomical abnormalities are already evident in the very early phase of psychosis (Wood *et al*. 2008) whereas longitudinal MRI studies found that the subset of patients who developed psychosis showed a longitudinal reduction in GM in the orbito-frontal, temporal lobe, parietal lobe and cerebellum (Pantelis *et al*. 2003; Job *et al*. 2005; Borgwardt *et al*. 2008).

Conclusions and future directions

Neuroimaging studies have provided compelling evidence that despite antipsychotic medication (both typical and atypical) there are detectable anatomical changes at the level of total and regional brain volumes. To date, it remains elusive whether the effects of antipsychotic medication on GM volume are simply

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beneficial. Experimental studies of macaque monkeys showed that chronic administration of either haloperidol or olanzapine was associated with smaller GM volume (Konopaske *et al*. 2008). These results, if confirmed, raise ethical questions on antipsychotic use. If antipsychotic medication may lead – at least in some patients – to GM volume reduction careful benefit–risk decisions have to be made for individual patients. Patients with schizophrenia should be very carefully informed about the potential risks (and of course benefits) of antipsychotic medication.

It is questionable whether the effects we are observing are the direct effects of antipsychotics or due to the illness process. Until we have more reliable studies from non-medicated patients, the potential impact of the confounding effect of medication must be borne in mind. For future studies, we therefore suggest focusing on longitudinal designs that represent the gold standard for investigation of medication effects. These studies clearly have the advantage of powerful, within-subject designs. Small sample sizes, heterogeneity in the sociodemographic characteristics of subjects, and lack of consistency between scanning parameters should be addressed by future multi-site studies that have shown the potential to overcome most of these problems and to bridge basic neuroscience with clinical psychiatry. So far, the investigation of patients at risk or with a first episode of schizophrenia seems to be the most promising alternative.

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Declaration of Interest

None.

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Letters to the Editor

Hippocampal volume reduction specific for later transition to psychosis or substance-associated effects?

We read with great interest the article by Witthaus and colleagues[1] recently published in the *Journal of Psychiatry and Neuroscience*. The authors found that, compared with controls, patients at ultra-high risk (UHR) had significantly smaller volumes of the hippocampus corpus and tail bilaterally. The UHR patients who later developed psychosis had smaller right hippocampus corpus and tail volumes than did those who did not develop psychosis. The authors concluded that the hippocampal volume reduction may be indicative of the prodromal phase of schizophrenia and may represent a risk factor for transition into psychosis.

However, significantly reduced (right) hippocampal volumes in UHR patients with later transition are in contrast to previous region-of-interest studies. We and others[2,3] showed no volumetric hippocampal differences between converters and nonconverters, suggesting that hippocampal volumes are not related to an at-risk mental state with later transition to psychosis. Instead, there is evidence for hippocampal and parahippocampal volume reductions developing as the disease progresses, at least during the first psychotic episode.[4,5]

These inconsistent results may be attributable to different ascertainment strategies, transition criteria, clinical follow-up periods, cannabis abuse and medication effects.[6] Witthaus and colleagues[1] reported that within 9 months after magnetic resonance imaging, 2 UHR patients made the transition to psychosis, and 6 patients were lost to clinical follow-up and therefore considered to be converters (assumption based on available clinical information). In contrast to our and other previous neuroimaging studies, patients at high risk of psychosis were followed-up for at least 1 year, and standardized criteria[7] were applied to determine if any patients made the transition to psychosis.

In addition, Witthaus and colleagues[1] did not report complete information on the medication status of the UHR patients. They stated that 11 of 29 patients had received atypical antipsychotics, alluding to short-term risperidone or olanzapine treatment. However, it is unclear whether those at UHR who later transitioned to psychosis received more or less antipsychotics compared with UHR patients who did not transition.

This raises the question as to whether the volumetric alterations seen in the UHR group could be an effect of antipsychotic medication. We agree with the authors that the results of the study cannot simply be explained by an effect of antipsychotic medication taken only for an average of 1.9 days. However, 2 recently published systematic reviews on the effects of antipsychotics on the brain concluded that antipsychotics may contribute to brain structural changes observed in psychosis and that their effects are regional rather than global.[8,9]

Moreover, UHR individuals with cannabis abuse were included if their psychotic symptoms began before the onset of cannabis abuse. However, recently published studies have shown an intrinsic influence of cannabis on brain structure and function.[10,11] There is evidence that the degree of acute psychotic symptoms following tetrahydrocannabinol administration modulated mediotemporal function among healthy men.[11] Furthermore, continuous cannabis use over 5 years led to progressive loss of brain volume among first-episode schizophrenia patients.[10]

Therefore, it would have been interesting to perform a statistical analysis covarying for effects of cannabis use or to compare hippocampal volumes in UHR patients with and without cannabis abuse. This could address the putative effect of cannabinoids on the hippocampus.

Despite the fact that neuroimaging studies have provided evidence that, independent of psychotropic substances, there are detectable anatomic abnormalities at the level of total and regional brain volumes, the effects of cannabis and antipsychotics on hippocampal volume remain elusive. Until we have reliable UHR studies addressing the longitudinal effects of psychotropic substances on brain structures as the hippocampus, we must keep the potential impact of substance-associated effects in mind.

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Hippocampal alterations in ultra-high risk patients are independent from medication and cannabis use

In their comment on our article entitled "Hippocampal subdivision and amygdalar volumes in patients in an at-risk mental state for schizophrenia,"[1] Borgwardt and colleagues raise some critical questions regarding our finding that hippocampal volume loss is related to an at-risk mental state. Instead, they argue that smaller right hippocampus corpus and tail volumes in ultra-high risk patients (UHR) who later developed schizophrenia compared with those who did not develop schizophrenia may be attributable to cannabis abuse and/or medication effects.

In fact, in our sample, one patient who transitioned into psychosis was taking antipsychotic medication and 7 who transitioned had never taken an antipsychotic. In comparison, in the UHR group that did not transition, 10 were taking antipsychotic medication and 11 were not. Notably, there was no significant difference in right hippocampal corpus and tail volume between these 4 groups ($F_{3,27} = 0.668$, $p = 0.58$).

Among the UHR patients who transitioned into psychosis, only 1 had previous cannabis abuse (see the 3-month criterion we used[1]), whereas 7 did not use cannabis. Among the UHR patients who did transition, 8 had comorbid cannabis abuse and 13 were free of cannabis abuse. Again, when we compared the volumes of the right hippocampal corpus and tail, we found no significant difference between the groups ($F_{3,27} = 1.146$, $p = 0.35$).

These findings suggest that the differences in the volume of the hippocampus corpus and tail between UHR patients who transitioned into psychosis and those who did not could not be accounted for by the effect of antipsychotic medication or cannabis abuse. Although 2 previous studies did not reveal hippocampal volume differences between converters and nonconverters,[2,3] we believe that it would be premature to rule out anatomic abnormalities in UHR states in these brain regions. Our study indicates that hippocampal volume reduction may precede the onset of schizophrenia and may be present in prodromal stages, independent of medication effects or the presence or absence of cannabis abuse.

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Letter to the Editors

Superior temporal gray and white matter changes in schizophrenia or antipsychotic related effects?

Dear Editors,

We read with great interest the article by Lee et al recently published in Schizophrenia Research (Lee et al., 2009). The authors found that as compared with controls, schizophrenic patients have reduced gray matter (GM) in the bilateral superior temporal gyrus (STG). Also, patients showed increased mean diffusivity, bilaterally in STG gray matter, and in left STG white matter (WM). In addition, mean diffusivity in left STG WM was positively correlated with auditory hallucinations and attentional impairments. They concluded that disruption of tissue integrity in STG WM and GM is a core feature in schizophrenia. Imaging studies of schizophrenia and schizotypal disorder (Takahashi et al., 2006) have repeatedly demonstrated volume differences in superior temporal gyrus and its subregions (Sun et al., 2009). In addition, there is evidence indicating a longitudinal reduction of superior temporal gyrus during transition from an at-risk mental state to psychosis (Borgwardt et al., 2008; Takahashi et al., 2009).

However, all 21 patients were medicated with antipsychotics. This raises the question as to whether the MRI and DTI alterations seen in the patient group could be an effect of antipsychotic medication. The authors argue that an effect of medication alone could not explain the observed findings. However, two recently published systematic reviews on the effects of antipsychotics on the brain concluded that antipsychotics may contribute to brain structural changes observed in psychosis, and that their effects are regional, rather than global (Navari and Dazzan, 2009; Smieskova et al., 2009). In particular, longitudinal VBM studies in patients with schizophrenia have indicated that treatment state can selectively affect GM volume in the superior temporal gyrus (McClure et al., 2006). In addition, Lee et al. (2009) have acknowledged that 5 subjects were taking typical antipsychotics, 15 atypical, and 1 both (mean dose in chlorpromazine equivalence was 418.2 mg/d, SD = 307.9). Recent MRI studies in first episode psychosis have showed a differential effect of typical and atypical antipsychotics on brain volumes, with typicals affecting more extensively the basal ganglia and cortical areas (including superior and middle temporal gyri) (Dazzan et al., 2005). Although the differential actions of antipsychotic type on the cortex are not well understood, there was a selective effect of antipsychotic type on the superior temporal gyral volume (McClure et al., 2006). The type of antipsychotic treatment may also differentially impact brain myelination and white matter volumes in adults with schizophrenia (Bartzokis et al., 2007). Unluckily complete information on the type of antipsychotic molecule was not available for the patient group. A previous longitudinal VBM investigation in neuroleptic-naïve first episode subjects showed that 6 weeks treatment with risperidone was associated with increased superior temporal gyral volume (Girgis et al., 2006). It would have been interesting to compare STG volumes in subjects treated with typical vs atypical to address the putative neuroprotective effect of atypical antipsychotics such risperidone in this brain area.

The potential impact of antipsychotic treatment on the findings reported by Lee et al. (2009) is an intrinsic difficulty even in longitudinal studies of subjects with a first episode of psychosis, 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 still meet ultra-high risk criteria, and are usually medication-free. This may reveal longitudinal changes that predate the onset of illness and that are not confounded by the effects of antipsychotic medication.

It was suggested that antipsychotic medication treatment remain a possible explanation for some of the STG volume reductions. However, it is questionable whether the effects observed are the direct effects of antipsychotics or whether the antipsychotic type or dose measured are actually surrogates for a third variable that is not measured (Borgwardt et al., 2009). Also, there could also be progressive brain change unrelated to medication as suggested from the early 1900's by many pneumoencephalographic studies. Neuroleptic treatment was not yet introduced when these studies begun, however, they showed that patients with chronic schizophrenia clearly had ventricular enlargement compared with controls (Haug, 1982; Huber, 1957; Jacobi and Winkler, 1927).

Despite neuroimaging studies have provided compelling evidence that independently of antipsychotic medication there are detectable anatomical changes at the level of total and regional brain volumes, it remains elusive whether the effects of atypical antipsychotic medication on GM and WM volume is neuroprotective and clinically beneficial. Unless we do not have more reliable UHR studies addressing the longitudinal effect of psychopharmacological treatments on brain structure, the potential impact of the confounding effect of antipsychotic medication has to be kept in mind.

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Contributors

SJB and PFP wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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Review

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

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ABSTRACT

Objectives: In early stage psychosis research the identification of neurobiological correlates of vulnerability to schizophrenia is an important hurdle.
Methods: We systematically reviewed the neuroimaging publications on high-risk subjects with subsequent transition to psychosis (HR-T) and conducted a meta-analysis calculating the effect size Cohen's d.
Results: Out of 30 identified studies 25 met the inclusion criteria. Structural (s)MRI 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). Meta-analysis revealed relatively larger whole brain volumes in HR-T compared to HR-NT subjects (mean Cohen's d 0.36, 95% CI 0.27–0.46). Compared to HR-NT, HR-T subjects showed in functional imaging studies reduced brain activation in prefrontal cortex, reduced neuronal density, and increased membrane turnover in frontal and cingulate 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.

Contents

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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 (Borgwardt et al., 2009; 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; Kanaan et al., 2009; 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 or the unaffected relatives of patients with normal controls (Baare et al., 2001; Borgwardt et al., in press; Ettinger et al., 2007; Hulshoff Pol et al., 2004; Job et al., 2003; Johnson et al., 2003; Lawrie et al., 1999, 2002; Lui et al., 2009b; 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 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 (Table 1 for review of selection criteria to define clinical high-risk groups). 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 (Broome et al., 2005a; Riecher-Rossler et al., 2007, 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, 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, diffusion weighted imaging (DWI)) and functional (fMRI, magnetic resonance spectroscopy (MRS) and positron emission tomography (PET)) approaches. Structural neuroimaging studies from FE schizophrenia subjects reported small reductions in global and regional gray and white matter volumes at initial presentation (Brambilla and Tansella, 2007; 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 less pronounced.

2. Methods

Firstly, we conducted a systematic review of neuroimaging studies on high-risk subjects. Secondly, in a meta-analytic approach we calculated (a) effect size separately for each study (b) mean Cohen's d for global brain volume measurements (whole brain volume (WBV), intracranial volume (ICV), gray matter volume (GMV)). To achieve a high standard of reporting we have adopted 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) guidelines (Moher et al., 2009) (Fig. 1) and the revised QUOROM Statements (Quality Of Reporting Of Meta-analyses) (Moher et al., 1999) because our included studies are mostly case–control 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 imaging, fMRI, structural magnetic resonance imaging, sMRI, positron emission tomography, PET, magnetic resonance spectroscopy, MRS, diffusion weighted imaging, DWI. Two reviewers (RS, SJB) 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 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 Section 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 were case–controlled studies and they had to have control subjects that were matched for age and sex. There was one pilot study (Pantelis et al., 2003) and three subsequent 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 Section 3.2). When the data from a single subject sample were reported in separate publications, these were treated as a single study. Conversely, a publication that reported two forms of different imaging data from the same subjects was considered as two studies.

2.2. Recorded variables

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 4).

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 medication. 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 was the ICV as a sum of the volume of all voxels designated as GMV, white matter volume plus cerebrospinal fluid and the WBV as a sum of gray matter plus white matter volume (Courchesne et al., 2000) recorded in 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 many 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 ($\geq .15$ and $<.40$), medium effect ($\geq .40$ and $<.75$), large effect ($\geq .75$ 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). Mean Cohen's d for global brain volume measurements (WBV, ICV, GMV) were calculated. For functional imaging studies and studies reporting regional volumes, mean Cohen's d was not calculated, because the available literature was too small and inconsistent to allow meaningful mathematical combination.

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. Although the studies differ methodologically, we did not found any difference in outcome-level assessment of risk of bias.

Table 1
Selection criteria employed to define clinical high-risk groups.

Criteria/Center (clinic) - Instruments	Melbourne (PACE)/London (OASIS) - CAARMS	Basel (FEPSY) - BSIP	Bonn/Düsseldorf/Cologne/Munich (GRNS) - BSABS, ERIRAOS
Attenuated Psychotic Symptoms (APS)[a]	BPRS: unusual thought content 2–3 BPRS: hallucinations 1–2 BPRS: suspiciousness 2–3 BPRS: conceptual disorganisation 1–3 CASH: delusions ≥ 2 Several times a week[b] ≥1 week[c]	BPRS: unusual thought content 2–3 BPRS: hallucinations 1–2 BPRS: suspiciousness 2–3 BPRS: conceptual disorganisation 1–3 CASH: delusions ≥ 2 Several times a week[b] ≥1 week[c]	BPRS: unusual thought content 2–3 BPRS: hallucinations 1–2 BPRS: suspiciousness 2–3 BPRS: conceptual disorganisation 1–3 CASH: delusions ≥ 2 Several times a week[b] ≥1 week[c]
Brief Limited Psychotic Symptoms (BLIPS)[a]	BPRS: unusual thought content ≥ 4 BPRS: hallucinations ≥ 3 BPRS: suspiciousness ≥ 4 BPRS: conceptual disorganisation ≥ 4 CASH: delusions ≥ 3 <1 week[b] Within the past year[c] Resolve spontaneously	BPRS: unusual thought content ≥ 4 BPRS: hallucinations ≥ 3 BPRS: suspiciousness ≥ 4 BPRS: conceptual disorganisation ≥ 4 CASH: delusions ≥ 3 <1 week[b] Within the past year[c] Resolve spontaneously	BPRS: unusual thought content ≥ 4 BPRS: hallucinations ≥ 3 BPRS: suspiciousness ≥ 4 BPRS: conceptual disorganisation ≥ 4 CASH: delusions ≥ 3 <1 week[b] Within the past year[c] Resolve spontaneously
Trait + state risk factor[a]	1st degree relatives, Significant reduction in mental state or functioning (reduction in GAF ≥ 30) within the past year	1st or 2nd degree relatives, defined number of risk factors, prodromes + marked deterioration in defined social roles	1st degree relatives, pre- or perinatal complication (reduction in GAF ≥ 30)
Basic symptoms	None	Additional unspecific risk[d] category assessed (not included in MRI studies) defined number of prodromes and/or risk factors (a.o. some basic symptoms)	BSABS: Thought interference, thought preservation, thought pressure, thought blockage; disturbances of receptive language, decreased ability to discriminate between ideas and perception, unstable ideas of reference (subject-centrism), derealisation, visual or acoustic perception disturbances In the last 3 months[c] Several times a week[b]

Abbreviations: BPRS, Brief Psychiatric Rating Scale; BSABS, Bonn Scale for Assessment of Basic Symptoms (Klosterkotter et al., 2001); BSIP, Basel Screening Instrument for Psychosis (Riecher-Rossler et al., 2007, 2008); CAARMS, Comprehensive Assessment of ARMS (Yung et al., 2005); CASH, Comprehensive Assessment of Symptoms and History; FEPSY clinic, Early detection of psychosis clinic; GAF, Global Assessment of Functioning; GRNS, German Research Network on Schizophrenia programme; ERIRAOS, Early Recognition Inventory based on Interview for the Retrospective Assessment of the Onset of Schizophrenia (Maurer and Hafner, 2007); OASIS, Outreach And Support In South London clinic; PACE, Personal Assessment and Crisis Evaluation clinic.
[a] APS, BLIPS, Trait + state risk factor - according to Yung et al. (1998).
[b] Frequency.
[c] Duration.
[d] Riecher-Rossler et al. (2007).

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, 2007) up to 54% (Criteria for Prodromal Syndromes (COPS)) (Miller et al., 2002) within 1 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, 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*

Table 2
Neuroimaging studies included in the review.

Center	Authors and year of publication	Specification		*n* subjects overlapping with[a]	HC			HR				HR-T			HR-NT			FE		
					n	M/F	Age	*n*	M/F	Age	bs/f-up med.	*n*	M/F	Age	*n*	M/F	Age	*n*	M/F	Age
Melbourne	Phillips et al. (2002)	sMRI-ROI	c-s	–	139	82/57	30.1	60	35/25	20	0	20	12/8	19.6	40	23/17	20.2	32	25/7	21.2
	Pantelis et al. (2003)	sMRI-VBM	c-s	–	–	–	–	75	n.a.	20.5	0/2	23	13/10	19.3	52	30/22	21.6	–	–	–
			l	–	–	–	–	21	n.a.	19.7		10	3/7	18.9	11	4/7	20.5	–	–	–
	Wood et al. (2003)	^{1}H MRS	c-s	–	21	13/8	34.1	30	17/13	19.5	0	6	–	–	14	–	–	56	36/20	21.7
	Yucel et al. (2003)	sMRI-ROI	c-s	15, Wood et al. (2003)	75	n.a.	29.1	63	63/0	19.2	0	21	n.a.	18.4	42	n.a.	19.9	n.a.	n.a.	n.a.
	Garner et al. (2005)	sMRI-ROI	c-s	–	49	32/17	20.2	94	58/36	19.6	0	31	20/11	19.1	–	–	–	–	–	–
	Wood et al. (2005)	sMRI-ROI	c-s	19, Phillips et al. (2002)	49	n.a.	23.6	35 HR+, 44 HR−	79/0	19.7 HR+, 20.6 HR−	n.a.	12 HR+, 12 HR−	–	–	–	–	–	–	–	–
	Velakoulis et al. (2006)	sMRI-ROI	c-s	60, Phillips et al. (2002)	87	55/32	26.9	135	78/57	20.1	0	39	24/15	19	96	54/42	20.6	162	108/54	21.5
	Thompson et al. (2007)	sMRI-ROI	c-s	–	–	–	–	23	14/9	18.9	0	5	–	–	–	–	–	–	–	–
	Fornito et al. (2008)	sMRI-ROI	c-s	–	33	21/12	21.00	70	41/29	19.6	13	35	21/14	19.3	35	20/15	19.9	–	–	–
	Sun et al. (2009)	sMRI-CPM	l	20, Pantelis et al. (2003)	–	–	–	35	19/16	19.9	0/2[b]	12	7/5	19.5	23	12/11	20.2	–	–	–
	Takahashi et al. (2009a)	sMRI-CPM	c-s	–	22	12/10	22	35	19/16	19.9	0/9[b]	12	7/5	19.5	23	12/11	20.2	20	16/7	21.6
			l	?, Pantelis et al. (2003), Sun et al. (2009)																
	Takahashi et al. (2009b)	sMRI-ROI	c-s	–	55	36/19	20.8	–	–	–	0/16[b]	31	20/11	19.1	66	39/27	20.2	–	–	–
			l	31 and 16, Sun et al. (2009) and Pantelis et al. (2003)	20	12/8	21.6	–	–	–		11	6/5	19.5	20	11/9	20.3	–	–	–
	Walterfang et al. (2008)	sMRI-VBM-WM	C-s	75, Pantelis et al. (2003)	–	–	–	75	n.a.	20.5	7	23	13/10	19.3	52	30/22	21.6	–	–	–
			l	21, Pantelis et al. (2003)	–	–	–	21	n.a.	19.7	0/5	10	3/7	18.9	11	4/7	20.5	–	–	–
Edinburgh	Harris et al. (2004)	sMRI-GI	c-s	–	–	–	–	30	20/10	21	n.a.	16	11/5	20.1	14	9/5	21.79	–	–	–
	Job et al. (2005)	sMRI-VBM	1	–	19	12/7	21	47 HR−, 18 HR+	34/31	21.4	0	8	n.a.	n.a.	–	–	–	–	–	–
	Marjoram et al. (2006)	fMRI	c-s	–	13	8/5	29.6	12	5/7	28.9	3	5	1/5	26.8	–	–	–	–	–	–
	Whalley et al. (2006)	fMRI	c-s	–	21	13/8	36.8	41 HR−, 21 HR+	26/36	27.0 HR−, 25.5 HR+	0	4	3/1	22.8	–	–	–	–	–	–
	Harris et al. (2007)	sMRI-GI	c-s	–	–	–	–	145	72/73	20.74	n.a.	17	11/6	20.18	128	61/67	21.3	–	–	–
Basel	Borgwardt et al. (2007a)	sMRI-VBM	c-s	–	22	13/9	23	35	22/13	23.7	3	102	9/3	24.6	23	13/10	23.3	25	18/7	27.1
	Borgwardt et al. (2007b)	sMRI-VBM	c-s	–	22	13/9	23	–	–	–	1	12	9/3	24.6	–	–	–	25	18/7	27.1
	Borgwardt et al. (2008a)	sMRI-VBM	1	–	–	–	–	20	12/8	24.7	5/1	10	7/3	25.2	10	5/5	24.2	–	–	–
	Buehlmann et al. (2009)	sMRI-ROI	c-s	–	22	13/9	23	37	22/15	24.7	4	16	11/5	26.4	21	11/10	23.6	23	17/6	26.8
Munich	Koutsouleris et al. (2009b)	sMRI	c-s	–	75	46/29	25.1	20 E-HR, 26 L-HR	29/17	25.2	0	15	11/4	22.4	18	11/7	25.9	–	–	–
Bonn	Jessen et al. (2006)	^{1}H MRS	l	–	31	14/17	34.8	10 E-HR, 9 L-HR	9/10	27.0 E-HR, 28.7 L-HR	2[b]	3 (2 from E-HR)	n.a.	n.a.	16	n.a.	n.a.	21	2/19	33.4
	Hurlemann et al. (2008)	PET	c-s	–	21	13/8	26.8	6 E-HR, 8 L-HR	10/4	25.8 E-H/ 27.5 L-HR	0	5 (from L HR)	n.a.	n.a.	9	n.a.	n.a.	–	–	–

Abbreviations: age, mean age in years; ARMS, at-risk mental state; bs, baseline; bs/f-up med., *n* medicated HR in baseline/follow-up; CPM, cortical pattern matching; c-s, cross-sectional; E-HR, early HR; FE, first episode; fMRI, functional magnetic resonance imaging; f-up, follow-up; GI, gyrification index; GMV, gray matter volume; HC, healthy controls; HR-T, high-risk transition; HR-NT, high-risk without transition; HR+, positive family history of psychosis; HR−, negative family history of psychosis; ICV, intracranial volume; L-HR, late HR; l, longitudinal; M/F, males/females; MRS, magnetic resonance spectroscopy; *n*, number of subjects; n.a., not applicable; PET, positron emission tomography; ROI, region of interest; sMRI, structural magnetic resonance imaging; VBM, voxel-based morphometry; WBM, whole brain volume; WM, white matter.

[a] Studies are overlapping within centers.

[b] No complete information on medications.

Table 3
Structural imaging studies of individuals at high-risk of psychosis.

Center/population	Authors and year of publication	Specification		Medication	f-up (months)	Transition rate (%)	HR-T vs. HC[a] region, Talairach coordinates, cluster size	HR-T vs. HR-NT[a] region, Talairach coordinates, cluster size	HR-T vs. FE[a] region, Talairach coordinates, cluster size
Melbourne/UHR-PACE	Phillips et al. (2002)	ROI	c-s	Yes	12	33	No diff in hippocampal volume	↑: L hippocampal volume	↑: L hippocampal volume
	Pantelis et al. (2003)	VBM	c-s	No	24	31	Not studied	↓ GMV in R MTC, 29 −24 −17, kE = 270 R LTC, 49 2 −11, kE = 300 R IFC, 32 18 −9, kE = 142 ACG and PCG, 2 −29 28, kE = 2222	Not studied
		VBM	l	Yes	12	n/a	Not studied	↓ GMV in. L MTC, −31 −42 −25, kE = 416 L cerebellum, −41 −65 −25, kE = 216 CG, 1 −14 28, kE = 221 L OFG, −17 60 −23, kE = 171 ↑ GMV in R cuneus, 7 −74 19, kE = 127	Not studied
	Yucel et al. (2003)	ROI	c-s	No	12	33	Not studied	No diff in the CS continuity, PCS morphology or PCS asymmetry	Not studied
	Garner et al. (2005)	ROI	c-s	No	12	33	↑ pituitary volume	↑ pituitary volume by 12%	Not studied
	Wood et al. (2005)	ROI	c-s	Yes	12	30	Not studied	No diff in WBV, hippocampal or ACC volume	Not studied
	Velakoulis et al. (2006)	ROI	c-s	No	13	29	No diff in hippocampal or amygdala volume	UHR-T as well as UHR-NT normal hippocampal + amygdala volumes	Not studied
	Thompson et al. (2007)	ROI	c-s	No	24	22	Not studied	↓ plasma cortisol levels no relationships between cortisol plasma levels or number of glucocorticoid receptors and WBV or hippocampal or pituitary volumes	Not studied
	Fornito et al. (2008)	ROI	c-s	13	13–44	28	↓ thickness of bilateral rostral paralimbic ACC	↓ thickness of the rostral limbic ACC rostral paralimbic ACC subcallosal limbic ACC subcallosal paralimbic ACC	Not studied
	Sun et al. (2009)[b]	CPM	l	2	12	34	Not studied	↑ brain surface contraction in R PF region	Not studied
	Takahashi et al. (2009a)[b]	CPM	c-s l	9 f-up	20	34	↓ PT male HR-T vs. HC ↓ GM in L PP, L+R PT, L STG	No diff in STG GMV ↓ GMV in L PP, L PT	↑ caudal STG No diff
	Takahashi et al. (2009b)[b]	ROI	c-s 1	No 16 f-up	12 12–48	32 35	↓ short insula R ↓: insula by 0.4%/year	↓ GM in L, R insula ↓ GM in insula by 0.6%/year	Not studied Not studied
	Walterfang et al. (2008)	VBM	c-s	7	24	31	Not studied	↓ WMV in F-O fasciculus (L PMC), −27 −16 31, kE = 175 L frontal operculum close to longitudinal fasciculus, −29 3 27, kE = 107	Not studied
		VBM	l	5	12	n/a	Not studied	↓ WMV in L F-O fasciculuc (−23 −37 18) kE = 78 R optic radiation (5 −67 11.5) kE = 114 inferior cerebellum (−21 −69 −36) kE = 102 and (8 −42 −40) kE = 153	Not studied

Edinburgh/GHR-EHRS	Job et al. (2005)	VBM	l	No	28	12	Not studied	bs: no diff progressive: ↓ in GMD in L ITG, −51.1 −16.1 −31.2 L uncus, −24.6 −10.2 −28.9 R cerebellum, 40.6 −44.6 −381	Not studied
	Harris et al. (2004)	GI	c-s	n.a.	Up to 60	53	Not studied	↑ R PFC GI	Not studied
	Harris et al. (2007)	GI		n.a.	Up to 60	13	Not studied	↑ R PFC A-GI; ↑ R PFC GMV, no WM diff	Not studied
Basel/ARMS	Borgwardt et al. (2007a,b)	VBM	c-s	3	25	34	↓ GMV in L CG, −13.7 −26.9 40 R CG, 3.1 −44.6 40 L precuneus, −1.6 −47.7 51 L precuneus, −0.6 −50.2 50 R precuneus, 2.4 −48 55 L paracentral lobule, −2 −30.5 45 R paracentral lobule, 1.1 −39 65 L parietal lobule, −8.6 −68.5 55 ↑ GMV in Supramarginal G, −55 −44.5 25.1	↓ GMV in R insula, 41.6 12 2.2, kE = 881 IFG, 36.4 17.8 −4, kE = 32 STG, 49.5 4.2 −1, kE = 57 ↑ GMV in parahippocampal, fusiform, MOG + TC, IPC, −54.8 −45.9 16.5, kE = 3023 L red Nc. + thalamus, −0.4 −28.2 −5.5, kE = 2 096 R supramarg. gyrus, 52.3 −52.4 23.8, kE = 1408	n.s.: ↑ GMV in L STG, −55.1 −40.5 13.5 R STG, 55.5 −59.2 16.0 R ITG, 55.7 −56.3 −6 L ITG, −54.2 −60.4 −8 L MOG, −52.6 −62 −6.1 L MTG, −54.5 −35.5 4, R MTG, 58.5 −56.3 −1 fusiform gyrus L, −43.7 −69.1 −16 and R, 53.2 −54.4 −16 n.s.: ↓ GMV in R lentiform nucleus (14.8 9.7 −10.4)
	Borgwardt et al. (2008a)	VBM	l	5 bs, 1 f-up	36–48	n/a	Not studied	↓ GMV in OG, 14 28 −23 R SFG, 24 46 31 ITG, 48 −24 22 medial and superior parietal G, 32 −56 53 cerebellum, 8 −56 −24 L precuneus, −16 −80 39 rectal G, −4 28 −25	Not studied
	Buehlmann et al. (2009)	ROI	c-s	4	25	43	No diff	No diff in hippocampus	Not studied
Munich/ARMS	Koutsouleris et al. (2009a,b)	VBM	c-s	No	48	45	↓ GMV in R ACC, R DLPFC, R VLPFC DMPFC, VMPFC, OFC	↓ GMV in DMPFC, ACC, OFC	Not studied

Abbreviations: ACC, anterior cingulate cortex; ACG, anterior cingulate gyrus; A-GI, automated gyrification index; ARMS, at-risk mental state; bs, baseline; CG, cingulate gyrus; CPM, cortical pattern matching; CS, cingulate sulcus; c-s, cross-sectional; diff, differences; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; EHRS, Edinburgh high-risk study; f-up, follow-up; F-O, fronto-occipital; G, gyrus; GI, gyrification index; GMD, gray matter density; GMV, gray matter volume; GHR, genetic high-risk; HC, healthy control; HR population, high-risk population; HR-NT, high-risk without transition; HR-T, high-risk with transition; IFC, inferior frontal cortex; IFG, inferior frontal gyrus; IPC, inferior parietal cortex; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; kE, cluster size; L, left; l, longitudinal; LTC, lateral temporal cortex; med., medication; MOG, middle occipital gyrus; MTC, medial temporal cortex; n.a., not applicable; Nc., nucleus; OFG, orbitofrontal gyrus; OG, orbital gyrus; PACE, Personal Assessment and Crisis Evaluation - Melbourne; PCG, posterior cingulate gyrus; PCS, paracingulate sulcus; PFC, prefrontal cortex; PMC, premotor cortex; PP, planum polare; PT, planum temporale; R, right; ROI, region of interest; STG, superior temporal gyrus; supramarg., supramarginal; TC, temporal cortex; UHR, ultra-high-risk; VLPFC, ventrolateral prefrontal cortex; VMPFC, ventromedial prefrontal cortex; VBM, voxel-based morphometry; WBV, whole brain volume; WMV, white matter volume; ↑, increase; ↓, decrease, reduction.

[a] Where available region, Talairach coordinates, cluster size.

[b] No complete information on medications.

Table 4
Neurofunctional imaging studies of individuals at high-risk of psychosis.

Center/Population	Authors and year of publication	Specification	Medication	f-up in months	Transition rate %	HR-T vs. HC region, Talairach coordinates, cluster size	HR-T vs. HR-NT region, Talairach coordinates, cluster size
Edinburgh/GHR-EHRS	Marjoram et al. (2006)	f MRI-ToM	3	n/a	21	Not studied	↓ regional activation R MFG, 26 17 34, kE = 191
	Whalley et al. (2006)	f MRI-HSCT	No	18	6	↓ regional activation R ACG, 2 28 −4, L M/O FG, −17 50 −16, −17 27 −3, kE = 1217 R lingual gyrus, 6 −56 0, PCG, −4 −32 28, 2 −48 14, kE = 1627 R anterior STG, 36 20 −32, 30 16 −36, R uncus, 25 9 −25, kE = 853 L anterior STG, −32 14 −26, −35 19 −24, L amygdala, −33 −5 −25, kE = 528 ↑ regional activation L IPL, −28 −40 46, −35 −46 51, −30 −36 55, kE = 366	↓ regional activation R ACG, 18 50 −16, L M/O FG, 8 55 −16 and L FG, 34 47 −9, kE = 892 R lingual gyrus, 6 −55 0 and L PCG, 7 −63 8, 14 −47 7, kE = 345
Bonn/ARMS	Jessen et al. (2006)	^{1}H MRS	2	12	16	Not studied	↑ Cho/Cr in ACG ↓ NAA/Cho in ACG no diff NAA/Cr
	Hurlemann et al. (2008)	PET	No	18	36	↓ R caudate 5-HT$_{2A}$R BP by 62.2%	↓ in R caudate 5-HT$_{2A}$R BP by 60.7%
Melbourne/UHR-PACE	Wood et al. (2003)	^{1}H MRS	No	12	20	Not studied	No diff trend ↑: NAA/Cho in MTC

HR-T vs. FE, was not studied in any of included studies.

Abbreviations: ACG, anterior cingulate gyrus; ARMS, at-risk mental state; Cho, choline containing compounds; Cr, creatin; diff, difference; EHRS, Edinburgh high-risk study; FE, first episode; FG, frontal gyrus; HC, healthy control; HR-T, high-risk with transition; HR-NT, high-risk without transition; HSCT, Hayling Sentence Completion Task; GHR, genetic high-risk; IPL, inferior parietal lobule; L, left; MFG, middle frontal gyrus; M/O FG, medial/orbital frontal gyrus; MRS, magnetic resonance spectroscopy; MTC, medial temporal cortex; NAA, N-acetylaspartate; PCG, posterior cingulate gyrus; PET, positron emission tomography; R, right; STG, superior temporal gyrus; ToM, Theory of mind; 5-HT$_{2A}$R BP, serotonin binding potential; ↑, increase; ↓, decrease, reduction.

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).

3.2. Number of identified studies

As the approach of the selective comparison of HR-T versus HC, HR-NT and 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 Fig. 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; according to classification used by McGuire et al. (2008)), design of the study (cross-sectional/longitudinal), and cognitive task (Fig. 1, Table 2). The systematic review of the literature uncovered 20 structural imaging studies (i.e. MRI) and five functional imaging studies (two fMRI, two MRS and one PET). The total number of subjects included in the present review encompassed roughly 385 HR subjects, of whom 95 subsequently made a transition to psychosis (HR-T), 290 HC and 211 FE patients. The flowchart of the selection procedure with the included/excluded studies is summarized in Fig. 1 and was created on the template of the PRISMA flow diagram (Moher 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.

The results of our systematic review and meta-analysis are summarized below with respect to structural (Section 3.4) and functional (Section 3.5) 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 data analysis methods: seven studies used voxel-based morphometry (VBM), nine studies used region of interest (ROI), two studies used GI and further two used 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. (2004, 2007) have used hand-traced GI methodology in an older study, and later an automated GI (A-GI) methodology of prefrontal cortex folding. CPM encodes both gyral patterning and gyral-matter variation (Thompson et al., 2004). This is a 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 white matter.

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 GMVs of HR-T versus HR-NT found less GMV in right hippocampal, parahippocampal and cingulate cortex, lateral temporal and inferior frontal cortex at baseline (Pantelis et al., 2003).

Table 5
Meta-analysis of structural findings.

Authors and year of publication	Temporal cortex						Cingulate cortex				Prefrontal cortex		Insula		Cerebellum		WBV, ICV, GMV		
	medial			superior			anterior		posterior										
HR-T vs	HR-NT	HC	FE	HR-NT	HC	FE	HR-NT	HC	HR-NT	HC	HR-NT	HC	HR-NT	HC	HR-NT	HC	HR-NT	HC	FE
Phillips et al. 2002	↑ 0.37 - 0.76	↓ 0.4	↑ 0.4																
Pantelis et al. 2003	↓			↓			↓		↓		↓		↓						
	↓						↓				↓				↓				
Yucel et al. 2003							↔	↔	↔	↔									
Wood et al. 2005	↔						↔											↔	
Velakoulis et al. 2006 [a]	↑ 0.09 - 0.21	↓0.1 - 0.17	↑ 0.2 - ↓ 0.45														↑ 0.37	↓ 0.07	↑ 0.38
Thompson et al. 2007	↔																		
Fornito et al. 2008 [b]							↓ 0.4	↓ 0.596											
Sun et al. 2009											↓								
Takahashi et al. 2009a				↓ 0.03	↔ 0.01	↑ 0.42											↑ 0.49	↑ 0.6	↑ 0.63
				↓ 0.31	↓ 0.36	↑ 0.59											↑ 0.58	↑ 0.44	↑ 0.73
Takahashi et al. 2009b													↓0.11 - 0.72	↓0.13 - 0.78			↑ 0.39	↑ 0.11	
													↓	↓			↑ 0.33	↑ 0.43	
Job et al. 2005	↓														↓				
Harris et al. 2004 + 2007											↑ 0.51						↑ 0.4		
Borgwardt et al 2007a + b	↑	↑		↓	↑					↓	↓		↓				↑ 0.22	↓ 0.27	↑ 0.05
Borgwardt et al. 2008	↓										↓				↓				
Bühlmann et al. 2009[a]	↑ 0.08 - 0.23	↑ 0.01 - 0.26	↑ 0.24 - 0.84														↑ 0.11	↓ 0.13	↓ 0.13
Koutsouleris et al. 2009[c]							↓ 0.86	↓ 1.0			↓0.9	↓0.6 - 1.0							

Abbreviations: GMV, gray matter volume; HC, healthy control; HR-NT, high-risk without transition; ICV, intracranial volume; WBV, whole brain volume; ↑, increased; ↓, decreased; ↔, unchanged.
[a]No significant.
[b]For GMV no main effect of group, results for cortical thickness.
[c]Clusters: the largest effect sizes.
Green shading refers to relatively increased volumes in HR-T vs. HR-NT/HC/FE. Red shading refers to relatively decreased volumes in HR-T vs. HR-NT/HC/FE. Purple shading refers to similar or conflictive volumes in HR-T vs. HR-NT/HC/FE.

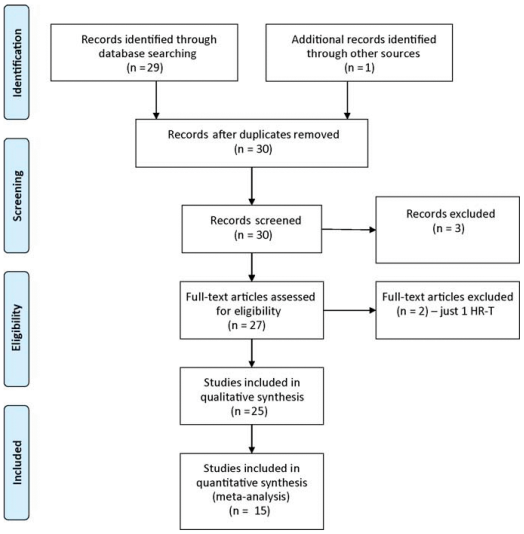

Fig. 1. Flowchart of the studies considered and included according to the design.

Studies by our own group showed that compared to HC, HR-T subjects had smaller GMVs 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 GMV 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 GMV in the superior temporal and inferior frontal gyrus and insula (Borgwardt et al., 2007b). 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 GMV 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 the already mentioned sample Pantelis et al. (2003) also studied progressive changes and found gray matter reductions in the left hemisphere in medial temporal, orbitofrontal, cingulate cortex and cerebellum.

Borgwardt et al. (2008a) 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 et al. (2009b) found longitudinal GMV reduction in superior temporal gyrus left in HR-T compared to HR-NT.

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 GMVs 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 GMV in superior temporal regions (Takahashi et al., 2009b).

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

3.4.1.4. Other studies. 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 et al. (2004) measured the hand-traced gyrification index and found increases in right prefrontal lobe GI values in HR-T individuals compared to HR-NT. 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 cannot (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.

3.4.2.1. 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. (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. Buehlmann et al. (2009) also failed to find volumetric differences in the hippocampus in HR-T versus HR-NT albeit in a smaller sample. No relationship between cortisol plasma levels and hippocampal volumes was observed in a cross-sectional study by 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).

3.4.2.2. 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). 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 et al. (2008) used a surface-based anterior cingulate parcellation 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.

3.4.2.3. 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).

3.4.2.4. Pituitary. 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. (2007) 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.

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 5). The study by 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 to the systematic review, however we could not calculate Cohen's d. Effect size was not calculated in another four studies (Wood et al., 2005; Yucel et al., 2003; Borgwardt et al., 2008a; Job et al., 2005) with insufficient information to provide effect size calculation.

The mean Cohen's d for all studies of WBV (Harris et al., 2004; Velakoulis et al., 2006), ICV (Takahashi et al., 2009a,b) and global GMV (Borgwardt et al., 2007b; Buehlmann et al., 2009; Takahashi et al., 2009a,b) revealed small to medium effect sizes (mean Cohen's d 0.36, 95% CI 0.27–0. 46) for larger global volumes in HR-T relative to HR-NT, but also compared to FE patients (Borgwardt et al., 2007b; Takahashi et al., 2009a; Velakoulis et al., 2006). Larger global volumes are 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 less GMV in HR-T compared to HC (Borgwardt et al., 2007b) (Table 1).

Compared to HR-NT, HR-T subjects showed relatively reduced regional GMV 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., 2008a; Pantelis et al., 2003; Sun et al., 2009) and cerebellum (Borgwardt et al., 2008a; Job et al., 2005; Pantelis et al., 2003) with small to large effect sizes (Table 1). 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 more GMV in right prefrontal cortex in HR-T compared to HR-NT (Harris et al., 2004) (Fig. 2).

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 PET study (Hurlemann et al., 2008) had focused on the availability of the cerebral serotonin (5-HT) receptor in naive HR subjects. Finally, two 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.

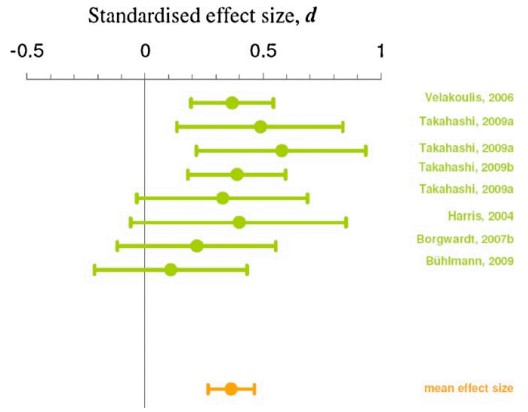

Fig. 2. Mean effect size (Cohen's d) and confidence interval (95% CI) of whole brain volume (WBV) (Velakoulis et al., 2006; Harris et al., 2004), total intracranial volume (ICV) (Takahashi et al., 2009a,b) and total gray matter volume (GMV) (Takahashi et al., 2009a,b; Borgwardt et al., 2007b; Buehlmann et al., 2009) comparing subjects with subsequent transition to psychosis (HR-T) and those without transition (HR-NT). Positive Cohen's d indicates relatively more WBV/ICV/GMV in HR-T compared to HR-NT.

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 the ability to understand a joke, 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. (2008) 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.

Using MRS, the HR-T subjects showed reduced NAA/Cho ratio as compared to HR-NT, suggesting an impaired neuronal density and function. 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. (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).

Table 6
Meta-analysis of functional findings.

Cente / Population	Authors and year of publication	Prefrontal cortex		Cingulate cortex		Temporal cortex		Parietal lobule		Occipital lobe	
	HR-T vs	HR-NT	HC	HR-NT	HC	HR-NT	HC	HR-NT	HC	HR-NT	HC
Edinburgh	Marjoram et al. 2005	↓ 0.6									
	Whalley et al. 2006		↓	↓	↓		↓		↑	↓	↓
Bonn	Jessen et al. 2006			↑ 1.56: Cho/Cr	↓ 1.72: NAA/Cho						
	Hurlemann et al. 2008[a]	↓ 1.51	↓ 1.45								
Melbourne	Wood et al. 2003[b]					↑ 0.96					

Abbreviations: Cho, choline containing compounds; Cr, creatin; HC, healthy control; HR-T, high-risk with transition; HR-NT, high-risk without transition; NAA, N-acetylaspartate; ↑, increased; ↓, decreased.
[a]Caudate serotonin binding potential.
[b]No sign. $p = 0.054$.
Green shading refers to relatively increased activation in HR-T vs. HR-NT/HC. Red shading refers to relatively decreased activation in HR-T vs. HR-NT/HC.

3.5.3. Meta-analysis of functional imaging studies

We have calculated Cohen's d in 4 out of 5 included functional imaging studies (Table 6). 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 5), 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).

4. Discussion

With this study we aimed to review the neuroimaging predictors of transition to psychosis. We investigated 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 HR-T already before transition to psychosis compared to HR-NT.

The present meta-analysis showed small to medium effect size of more whole brain volume and total GMV 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 larger WBV could indicate a dynamic process during the transition phase to psychosis, presumably affecting various cortical areas at approximately identical time points. It could reflect an effort to engage other, probably volumetrically larger, regions aiming to compensate commencing pathological processes. The apparently contradictory findings of larger whole brain volumes and regional gray matter volume reductions, can simply signify differences in tissue behaviour, i.e. tissue swelling or shrinkage, or involve changes in the cell density or composition of the neuropil and/or the myelinated sheets of neurons. It emphasizes the importance of understanding the role of the different brain tissue elements in the dynamics of brain volume changes.

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).

The present review and meta-analysis 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 psychosis may emerge as psychosis develops.

The present findings of fMRI revealed the decreased activation in prefrontal areas and increased activation in connected brain regions which 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 GMV in orbitofrontal, cingulate and parahippocampal areas (Pantelis et al., 2003) longitudinally in identical HR-T versus HR-NT population. These findings correspond to the growing evidence that dysfunction of integrated networks of brain regions is involved in antipsychotic-naïve patients with first-episode schizophrenia (Tregellas, 2009). It will be useful to combine structural and functional neuroimaging methods with evaluation of brain functional connectivity. Lui et al. (2009a) attempted to understand the relationship of GMV differences, functional connectivity and clinical measures in a recent study of FE matched with HC. They found that the functional networks involving the right superior temporal gyrus and middle temporal gyrus were associated with clinical symptom severity in antipsychotic-naïve FE patients.

These observations are of considerable 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 (SVMs). They have achieved fairly high accuracy, sensitivity and specificity in their prediction to psychosis based on the pattern of GMV 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., 2009a).

4.2. Methodological issues and limitations 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, limiting not only comparison of their results, but also mathematical combination of all studies results together.

There is a variety of neuroimaging techniques to investigate structural differences between the groups of HR individuals bringing afterward results in terms of abnormalities in GMV, density, thickness, contraction or asymmetry. Cytoarchitectural abnormalities as number of dendrites, dendritic spines and/or changes in neuronal myelination cannot be quantified directly in imaging data. Therefore, to date, neuroimaging provides limited informative value on those changes. The compared literature, however, reflects state of the art methodology of neuroimaging.

In this systematic review and meta-analysis we uncovered a large difference in secondary variables across studies (i.e. gender, medication, comorbidities, handedness), 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). In future, resting-state fMRI, a novel technique, has several potential advantages over task-activation fMRI in terms of its clinical applicability and reproducibility (Greicius, 2008; Lui et al., 2009c).

Another limitation of this comparative approach is that 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. Furthermore, differences in scanning parameters, image analysis and packages may also account for inconsistencies in neuroimaging measures (Fusar-Poli et al., 2008, 2010).

In addition, it is difficult to state whether the observed structural brain changes simply reflect normal inter-individual variation of brain anatomy (Luders et al., 2006), or signify 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 (Konopaske et al., 2008; Reinke et al., 2004). Recently published studies have shown intrinsic influence of cannabis to human brain structure and function (Rais et al., 2008; Bhattacharyya et al., 2009, 2010; Fusar-Poli et al., 2009b,c; Borgwardt et al., 2008b).

Antipsychotic medication is an important point, because 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; Haller et al., 2009; Borgwardt et al., 2006; 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 of the development of psychosis. Neuroimaging studies of high-risk individuals 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 yet completely established, neuroimaging studies in prodromal subjects could provide the targets for early intervention that could potentially prevent a chronic clinical trajectory of the illness.

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Different transition probabilities to psychosis associated with insular volume abnormalities. A VBM study

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ABSTRACT

Background: Although individuals vulnerable to psychosis (ARMS) have brain volumetric abnormalities, structural alterations underlying different probabilities for later transition are unknown.

Aim: We investigated gray matter volume (GMV) abnormalities by comparing two groups: long-term (ARMS-LT) and short-term (ARMS-ST) ARMS.

Method: Using voxel-based morphometry (VBM), we examined 22 healthy controls (HC) together with 18 ARMS-ST and 16 ARMS-LT, clinically followed for 3 months and 4.5 years on average, respectively.

Results: The ARMS-ST had decreased bilateral insular and right middle temporal GMV compared to the ARMS-LT and this was positively correlated with functional decline. Compared to the HC, the ARMS-LT had higher right insular GMV. Insular and inferior-parietal alterations related to negative symptomatology in the ARMS.

Conclusion: GMV abnormalities within the ARMS are related to different transition probabilities. Volume loss in the insula is associated with a higher risk for transition to psychosis.

Declaration of interest: None.

INTRODUCTION

There is a growing evidence of magnetic resonance imaging (MRI) that subjects at high clinical risk for psychosis have structural abnormalities in the frontal, insular and temporal regions. More recently MRI studies have examined whether there are specific neuroanatomical differences between high-risk subjects who subsequently develop psychosis and those who do not (for a review and meta-analysis of voxel-based morphometry (VBM) studies in high risk subjects see (Fusar-Poli, et al. 2011; Smieskova, et al. 2010)). Structural deficits associated with transition to psychosis can be seen as vulnerability markers for developing schizophrenia (Riecher-Rössler, et al. 2009; Smieskova, et al. 2010) and are of crucial relevance to the field of preventive interventions in psychosis.

Early clinical intervention in psychosis has recently become a major objective of mental health services. Research at this stage is a potential way of investigating the mechanisms underlying psychosis, as the same individuals can be studied before and after the onset of illness, often with minimal confounding effects of previous antipsychotic treatment and illness duration. The identification of a clinical syndrome (an 'At Risk Mental State') that reflects an 'ultra-high clinical risk' predisposition to psychosis is fundamental to both clinical and research work in this area. Most transitions to psychosis in ARMS individuals were found in the first two years after baseline assessment and were much less probable later (Riecher-Rössler, et al. 2009; Yung, et al. 2007), suggesting rapid dynamic neurophysiological changes during the first two years of the pre-psychotic phases. Independent studies have confirmed complex neurophysiological changes underlying the prodromal psychotic phases involving not only brain structure but also cortical functioning and disrupted dopaminergic or glutamatergic neurotransmission (Hurlemann, et al. 2008; Jessen, et al. 2006). However, to our best knowledge no study has explicitly addressed potential neurobiological markers of different levels of risk across the prodromal phase. We separately investigated the ARMS individuals with a short or long duration of the ARMS. All these individuals fulfill the ARMS criteria (similar to the PACE criteria (Yung, et al. 1998)) at the time of scanning. In the first group (short-term ARMS, ARMS-ST) the scan was done at the time of ascertainment of the ARMS (within 3 months on average). According to published data the probability of developing psychosis in this groups is up to 20–40% over two years (Riecher-Rössler, et al. 2009; Yung, et al. 1998). In the second group (long-term ARMS, ARMS-LT) the scan was done on average 4.5 years of follow-up. Although at the time of the scan this group was still on the risk continuum to develop psychosis, according to the published data (Cannon, et al. 2008; Riecher-Rössler, et al. 2009; Yung, et al. 2007), the probability of developing subsequent psychosis was lower compared to ARMS-ST. Importantly, most of the ARMS individuals who made the transition (90.5%), did so in the first two years after the ARMS was ascertained. After these two years, only 3% of included ARMS individuals developed psychosis (Riecher-Rössler, et al. 2009). In a study by Yung, the vast majority of transitions occurred in the first two years (estimated hazard ratio 0.58) and there were significantly less transitions over time (estimated hazard ratio 0.07) (Yung, et al. 2007).

Our principal aim was to examine the neuroanatomical brain abnormalities associated with these two different transition probabilities. We also aimed at identifying putative neuroanatomical resilience factors

associated with a reduced risk of developing psychosis. Resilience, as the capacity to cope adequately with stressful events (Muller-Spahn 2008), was found impaired in psychotic individuals (van Os, et al. 2005). Finally we aimed at clarifying the correlation between structural alterations and clinical outcomes during the prodromal phases of psychosis.

METHODS

The ARMS is defined according to the PACE (Personal Assessment and Crisis Evaluation Clinic, Melbourne) criteria and requires individuals to present attenuated positive psychotic or brief limited intermittent symptoms that do not reach full psychosis threshold (Riecher-Rössler, et al. 2009) and/or functional decline and genetic risk. Psychopathological symptoms mentioned above are often associated with negative symptoms (Lencz, et al. 2004; Riecher-Rössler, et al. 2009) and subtle cognitive deficits (Brewer, et al. 2006; Riecher-Rössler, et al. 2009; Simon and Umbricht 2010). Individuals with an ARMS (ARMS-ST) have a 20–40% probability of developing a psychosis (Riecher-Rössler, et al. 2009; Yung, et al. 1998). On a clinical basis only, it is very difficult to distinguish individuals who will later become psychotic from those who will not (McGorry, et al. 2003; Riecher-Rössler, et al. 2009).

Sample instruments

Since 1999, the Early Detection of Psychosis Clinic in Basel recruited and followed up the ARMS individuals over up to 7 years (Riecher-Rössler, et al. 2009). We assessed subjects using the 'Basel Screening Instrument for Psychosis' (BSIP), the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Negative Symptoms (SANS) and the Global Assessment of Functioning (GAF) at the time of scanning. The BSIP evaluates 'prodromal' symptoms (according to DSM-III-R) occurring in the last 5 years; nonspecific 'prodromal' signs in the last 2 years; previous and current psychotic symptoms, psychosocial functioning over the last 5 years, substance dependency; and psychotic disorders among first and second degree relatives . We obtained current and previous psychotropic medication, alcohol, nicotine, cannabis, and other illegal drug consumption using a semi-structured interview adapted from Early Psychosis Prevention and Intervention Centre (EPPIC) Drug and Alcohol Assessment Schedule (www.eppic.org.au).

Study population

Inclusion to the ARMS required one or more of the following: a) "attenuated" psychotic symptoms b) brief limited intermittent psychotic symptoms (BLIPS) or c) a first-degree relative with a psychotic disorder plus a marked decline in social or occupational functioning.

Exclusion criteria were: history of previous psychotic disorder; psychotic symptomatology secondary to an 'organic' disorder; substance abuse according to ICD-10 research criteria; psychotic symptomatology associated with an affective psychosis or a borderline personality disorder; age under 18 years; inadequate knowledge of the German language; and IQ less than 70.

We divided the ARMS individuals (n=34) into two subgroups depending on the duration of the ARMS status since the baseline assessment. Thus, our ARMS-ST group had the MRI scan as soon as practicable,

on average within 0.22 years (SD=0.43). The ARMS-LT group consists of individuals who did not convert to psychosis over a longer follow up period of on average 4.62 years (SD=2.06) after first ascertainment. At time of scanning all the ARMS-ST and ARMS-LT individuals still fulfilled the criteria according to Yung et al. for the ARMS (Yung, et al. 1998) but, because of the difference in duration of the ARMS, had different probabilities of developing psychosis (Cannon, et al. 2008; Riecher-Rössler, et al. 2009; Yung, et al. 2008).

From the baseline assessment the ARMS-ST and ARMS-LT subjects were followed up by the clinical service and received psychiatric case management. At the time of the scanning all the ARMS individuals (from both groups) were antipsychotic-naïve, except for one ARMS-ST subject (olanzapine 2.5 mg/day during 4 months before the scan) and two ARMS-LT subjects (medicated at the time of the scan, 1 zuclopenthixol 3x40 mg/day, and 1 aripiprazole 5mg/day, for unknown period prescribed for treatment of negative symptoms from their physician). Furthermore, 8 of ARMS-LT and 6 of ARMS-ST were receiving antidepressants at the time of the MRI scan.

We recruited healthy volunteers (HC, n=22) from the same geographical area as the other subjects. All subjects were representative of the local population of individuals presenting with an ARMS in terms of age, gender, handedness, IQ, and alcohol and cannabis consumption. These individuals had no current psychiatric disorder, no history of psychiatric illness, head trauma, neurological illness, serious medical or surgical illness, substance abuse, and no family history of any psychiatric disorder as assessed by an experienced psychiatrist in a detailed clinical assessment.

Data collection

MRI data were collected as part of the FEPSY (*Früherkennung von Psychosen* - Early Detection of Psychosis) study that is described in detail elsewhere (Riecher-Rössler, et al. 2009). Briefly, we recruited subjects with an ARMS in our specialized clinic for the early detection of psychosis at the Psychiatric Outpatient Department, Psychiatric University Clinics Basel, Switzerland. All the ARMS individuals were assessed at baseline and at the time of MRI scan.

Data analysis

Expanding on previous VBM studies in ARMS (meta-analysis (Fusar-Poli, et al. 2011)), here we investigated an ARMS-LT group with a lower probability of developing psychosis compared to the ARMS-ST group (Yung, et al. 2007). Additionally, we focused on the association between gray matter volume (GMV) and clinical measures.

On the basis of previous findings, we tested the following hypotheses:

1. The magnitude of volumetric abnormalities would be in parallel with the clinical status (ARMS-LT<ARMS-ST) compared to the healthy control (HC) group.

2. Regions with different gray matter volume in ARMS-LT compared to ARMS-ST would be associated with resilient factors playing a protective role in the process of psychosis.

3. Significant correlations between GMV and psychotic symptoms or global functioning were expected in the regions showing volumetric differences in ARMS.

Magnetic resonance image acquisition

Structural MRI

3D T1-weighted MPRAGE sequence on a 3T scanner (Siemens Magnetom Verio, Siemens Healthcare, Erlangen, Germany) was applied with 1x1x1 mm^3 isotropic spatial resolution and with inversion time of 1000ms, TR of 2s and TE of 3.4ms. All the scans were screened for gross radiological abnormalities by an experienced neuroradiologist.

Image analysis

We examined group-related differences in gray matter volume using the SPM8 software (http://www.fil.ion.ucl.ac.uk/spm; Wellcome Department of Cognitive Neurology, London, United Kingdom) running under Matlab 7.1 (Math Works, Natick, MA, USA). T1-weighted MPRAGE images were pre-processed using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm8/). This approach involves the creation of a study-specific template and the segmentation of each individual image using such template, with the aim of maximizing accuracy and sensitivity (Yassa and Stark 2009). We provided following steps: (1) checking for scanner artifacts and gross anatomical abnormalities for each subject; (2) using New Segmentation approach with different treatment of the mixing proportions; (3) using the DARTEL toolbox to produce a high-dimensional normalization protocol (Ashburner 2007); (4) checking for homogeneity across the sample; and (5) using 8 mm standard smoothing. We identified 2 subjects with mean covariance below two standard deviations and afterwards carefully screened their volumes, but found no artifacts and the quality of images was reasonable. We repeated the analyses without these two subjects, with the same results. That is why we decided not to exclude them from the analysis. After this pre-processing, we obtained segmented, normalized, and smoothed data that were used for the statistical analysis.

We performed an analysis of covariance (ANCOVA) to compare gray matter images from all 3 groups (ARMS-ST, ARMS-LT, HC). We modeled age, gender, and total gray matter volume as covariates of no interest to reduce the potential impact of these variables on the findings. Statistical significance was assessed at cluster-level using the non-stationary random field theory (Hayasaka, et al. 2004). The first step of this cluster-level inference strategy consisted of identifying spatially contiguous voxels at a threshold of $p<0.01$, uncorrected (cluster-forming threshold) (Petersson, et al. 1999). Statistical inferences were then made at $p<0.05$ after family-wise error (FWE).

To label the regions of brain activation MNI coordinates were transformed into Talairach space (www.ebire.org/hcnlab/cortical-mapping; Talairach Daemon software).

Correlation of GMV and clinical data

In addition to the whole-brain VBM analysis, correlation analyses were used to examine associations between GMV in areas where we found between-group volumetric differences. In order to examine the association between positive and negative symptoms and global functioning, we extracted gray matter values from the peak voxels (40 -18 6 and -56 -36 27) and from four subsidiary clusters with sphere 2mm

and performed a series of 2-tailed Pearson's correlation analyses using Statistical Package for the Social Sciences (SPSS 19.0) (supplementary table). Statistical threshold was set at $p<0.05$.

Statistical analysis of demographic data

We examined clinical and socio-demographic differences between groups using one-way analysis of variance (ANOVA), F-test, or chi-square test (Table 1). For post-hoc analyses we used multiple two-sided t-tests with Bonferroni correction. Statistical analyses were performed with the SPSS 19.0 and the level of significance was set at $p<0.05$.

Table 1: Demographic and clinical characteristic.

Characteristic	ARMS-ST (n=18)	ARMS-LT	HC (n=22)	Statistics	
Gender male (%)	14 (77.78%)	11(68.80%)	10 (45.45%)	$\chi2$=4.790	P=0.091
Mean age years	25.11 (6.15)	25.06 (2.30)	26.86 (4.00)	F=1.054	P=0.356
Handedness (left)	0	1 (6.25%)	1 (4.54%)	$\chi2$=1.061	P=0.588
MWT-B IQ	112 (14.13)	106 (12.38)	114 (9.45)	F=1.969	P=0.151
Years since presentation	0.22 (0.43)	4.62 (2.06)	0	F=78.590	P<0.000
Antipsychotics	0 (0%)	2 (12.50%)	0 (0%)	$\chi2$= 5.185	P=0.075
Antidepressants	6 (33.33%)	8 (50.00%)	0 (0%)	$\chi2$=13.33	P=0.001
Cigarettes/day	8.25 (9.89)	8.94 (11.86)	3.50 (6.76)	F=1.948	P=0.153
Alcohol currently				$\chi2$=5.044	P=0.283
no	2 (11.11%)	2 (12.50%)	1 (4.54%)		
moderate	7 (38.89%)	8 (50.00%)	16 (72.72%)		
drunkenness	9 (50.00%)	6 (37.50%)	5 (22.73%)		
Cannabis	7 (38.89%)	5 (31.25%)	4 (18.18%)	$\chi2$=2.509	P=0.285
BPRS total	40.06 (8.14)	32.67 (6.32)	24.55 (1.14)	F=35.980	P<0.000
Post-hoc	>HC: P<0.0001	>HC: P<0.0001			
	> ARMS-LT: P=0.001				
BPRS 9	2.47 (1.23)	1.73 (0.80)	1 (0)	F=16.020	P<0.000
Post-hoc	>HC: P<0.0001	>HC: P=0.027			
	> ARMS-LT: P=0.038				
BPRS 10	1.94 (1.20)	1.33 (0.90)	1 (0)	F=6.370	P=0.003
Post-hoc	>HC: P=0.002				
BPRS 11	2.29 (1.40)	1.53 (0.83)	1 (0)	F=9.930	P<0.000
Post-hoc	>HC: P<0.0001				
BPRS 15	1.65 (1.12)	1.27 (0.80)	1 (0)	F=3.560	P=0.031
Post-hoc	>HC: P=0.031				
APS	8.35 (3.32)	5.87 (2.26)	4 (0)	F=18.710	P<0.000
Post-hoc	>HC: P<0.0001	>HC: P=0.044			
	> ARMS-LT: P=0.007				
SANS total	21.00 (13.13)	10.53 (15.20)	0	F=18.080	P<0.000
Post-hoc	>HC: P<0.0001	>HC: P=0.016			
	>ARMS-LT: P=0.026				
GAF	61.29 (11.80)	75.33 (14.86)	88.27 (4.29)	F=32.880	P<0.000
Post-hoc	<HC: P<0.0001	<HC: P=0.003			
	<ARMS-LT: P=0.001				

Demographic and clinical characteristics with mean values and standard deviations in parentheses. For post-hoc analyses the Bonferroni corrections (at P=0.05) in SPSS 19.0 were calculated.
Abbreviations: APS - attenuated psychotic symptoms (APS = BPRS9 + BPRS10 + BPRS11 + BPRS15); BPRS – Brief Psychiatric Rating Scale: BPRS9 – suspiciousness, BPRS10 – hallucinations, BPRS11 – unusual thought content, BPRS15 – conceptual disorganization; GAF – Global Assessment of Functioning; MWT-B - multiple choice vocabulary IQ test (Mehrfachwahl-Wortschatz-Test Form B); SANS – Scale for the Assessment of Negative Symptoms

Table 2: Group differences in brain structure.

Contrast	P FWE	Cluster	P uncorr.	T	MNI	Region
ARMS-ST < ARMS-LT	0.036*	2532	0.001**	4.21	40 -18 6	R insula, BA 13
					54 -15 0	R STG, BA 22
					58 -6 -6	R MTG, BA 21
	0.401	1240	0.013	4.13	56 3 -24	R MTG, BA 21
					44 3 -32	R MTG, BA 21
	0.256	1484	0.008**	3.80	-56 -36 27	L IPL, BA 40
					-63 -42 42	L IPL, BA 40
					-46 -31 21	L Insula, BA 13
ARMS-ST>ARMS-LT	0.709	882	0.032	3.64	38 26 18	R IFG
					50 17 30	R MFG (BA 44, 45)
					48 26 16	R MFG (BA 45)
ARMS-ST < HC	0.475	1143	0.017	4.05	-34 44 24	L MFG, BA 10
					-32 56 21	L SFG, BA 10
					-28 29 27	L MFG, BA 9
	0.139	1806	0.004**	3.76	-3 18 -23	L Rectal G, BA 11
					2 21 -17	R Scal G, BA 25
					6 33 -17	R Scal, PAC G, BA
ARMS-LT>HC	0.235	1530	0.007**	4.02	36 -19 6	R insula
					34 -25 24	R Insula, BA 13
					39 -22 15	R Insula, BA 13
	0.549	1056	0.021	3.54	54 4 -24	R MTG, STG, BA 21
					46 20 -41	R STG, BA 38
					57 14 -32	R STG, BA 38
All ARMS < HC	0.460	1162	0.016	4.54	-30 30 27	L MFG, BA 9
					-32 56 21	L SFG, BA 10
					-33 45 22	L MFG, BA 10

Group differences in gray matter volume calculated from full factorial ANCOVA analysis using SPM8 with VBM8 toolbox with covariates age, gender, and VBM-GMV.

There were no significant differences in contrasts: ARMS-ST >ARMS-LT, ARMS-ST>HC, ARMS-LT<HC, ARMS-ST+ARMS-LT > HC.

* P value family-wise error (FEW) corrected P<0.05; ** P value uncorrected P<0.01

Abbreviation: ARMS-LT – long-term ARMS; ARMS-ST – short-term ARMS; BA – Brodmann area, HC – healthy controls; IPL – inferior parietal lobule, IFG – inferior frontal gyrus, MFG – middle frontal gyrus, MTG – middle temporal gyrus, PAC G –paracingulate gyrus, PL – parietal lobe, Scal G – subcallosal gyrus, SFG – superior frontal gyrus, STG – superior temporal lobe, WM- white matter

RESULTS

Clinical and demographic characteristics

There were no significant differences between the ARMS-ST, ARMS-LT and HC in age (P=0.356), gender (P=0.091), handedness (P=0.588), IQ (P=0.151), current alcohol (P=0.283) and cannabis (P=0.285) use. There were significant between group differences in positive and negative symptoms and in global functioning: The ARMS-ST group showed a higher total BPRS (P=0.001), attenuated psychotic symptoms (APS, P=0.007) and SANS (P=0.026) and lower GAF (P<0.001) scores compared to the ARMS-LT group. Both ARMS groups differed in these measures compared to the HC group significantly.

Gray matter volumes (VBM results)

Volumetric abnormalities in the ARMS vs. HC

The whole group of ARMS individuals compared to the HC showed less GMV in the left middle and superior frontal gyrus (table 2, P<0.05, uncorrected). The ARMS-ST group had less GMV than HC in the right subcallosal, paracingulate and left rectal gyri (table 2, P<0.01, uncorrected) and in the left middle and superior frontal gyrus (table 2, P<0.05, uncorrected). There were no regions where ARMS-ST had more GMV than HC. The ARMS-LT group had more GMV than the HC group in the right insula (table 2, P<0.01, uncorrected) and in the right middle and superior temporal gyrus (table 2, P<0.05, uncorrected). There were no regions were the ARMS-LT had less GMV than HC.

Volumetric abnormalities in the ARMS-LT vs. ARMS-ST

Compared to the ARMS-LT, the ARMS-ST group had less GMV in the right insula extending into the right superior and middle temporal gyrus (table 2, P<0.05, FWE corrected, figure 1 panel A) and in the left parieto-insular region (table 2, P<0.01, uncorrected, figure 1 panel B), and in the right middle temporal gyrus (table 2, P<0.05, uncorrected). The ARMS-ST had more GMV in the right inferior and middle frontal gyrus compared to the ARMS-LT (table 2, P<0.05, uncorrected).

Volumetric abnormalities across the three groups

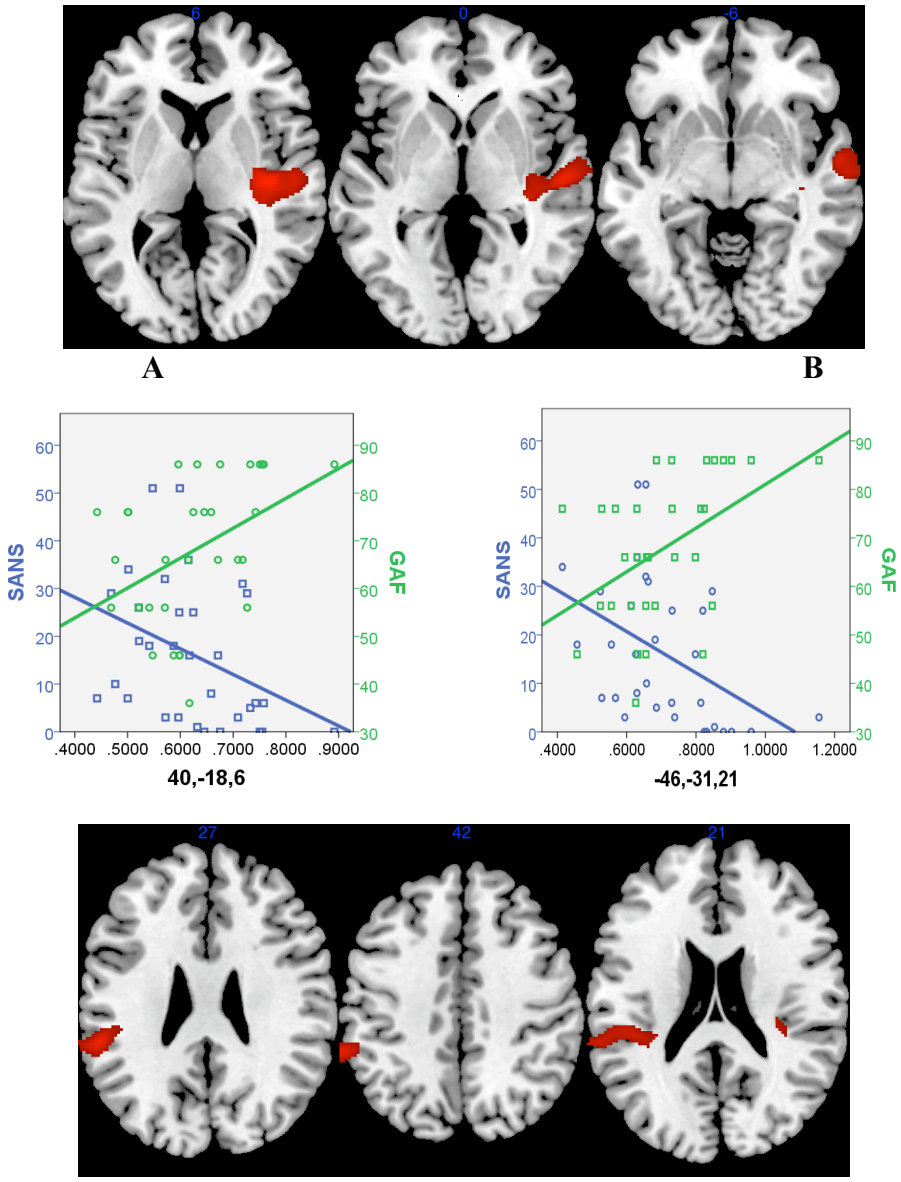
The direct comparison of GMV in the right insula (40 -18 6) across all three groups showed that the ARMS-ST group had less GMV than the HC and the HC less than the ARMS-LT (ARMS-ST<HC<ARMS-LT).

Correlation analyses of GMV and clinical outcomes

Within the whole ARMS group (ARMS-LT+ARMS-ST) there was a negative correlation (P<0.05) between negative symptoms (SANS score) and GMV in the right insula (40 -18 6, Pearson's correlation coefficient -0.376, figure 1), left insula (-46 -31 21, Pearson's correlation coefficient -0.445, figure 1), and in the left inferior parietal lobule (-56 -36 27, Pearson's correlation coefficient -0.381, supplementary

table). Functional decline (GAF score) correlated positively (P<0.01) with GMV in the right insula (40 -18 6, Pearson's correlation coefficient 0.446, figure 1), in the right superior temporal gyrus (54 –15 0, Pearson's correlation coefficient 0.451; 58 -6 -6, Pearson's correlation coefficient 0.348 at P<0.05) and in the left insula (-46 -31 21, Pearson's correlation coefficient 0.466, figure 1) within the whole ARMS group. We found no significant correlations between positive symptoms (BPRS score) and GMV (supplementary table). When the above correlations were repeated within the ARMS-LT and ARMS-ST we found a significant relationship only between GMV and GAF (P<0.05): negative correlation in the ARMS-ST group in the left inferior parietal lobule (-56 -36 27, Pearson's correlation coefficient -0.495, supplementary table) and positive correlation in the ARMS-LT group in the left insula and superior temporal gyrus (-46 -31 21, Pearson's correlation coefficient 0.612, supplementary table).

Figure 1: Correlation of psychopathology and GMVs within the ARMS group.



Correlation of psychopathology and gray matter volume (GMV) in two large clusters with less GMV in the ARMS-ST compared to the ARMS-LT.
The figures show the volumetric differences between ARSM-ST and ARMS-LT groups. The cluster in the figure above (A) comprising the right insula (40 -18 6) and extending into the right superior temporal gyrus (-50 -15 0) and right middle temporal gyrus (58 -6 -6) reflect decreased GMV in the ARMS-ST as compared to the ARMS-LT group (P<0.05 FEW corr.). Correlation of psychopathology and GMV in this cluster across the whole ARMS sample (ARMS-LT+ARMS-ST) (Pearson's correlation coefficient for SANS -0.376* and for GAF 0.446**) is shown in the middle diagram on the left.
The cluster in the bellow figure (B) comprising the left inferior parietal lobule (-56 -36 27 and -63 -42 42) and the left insula (-46 -31 21) reflect decreased GMV in the ARMS-ST as compared to the ARMS-LT group (P<0.01 uncorr.). Correlation of psychopathology and GMV in this cluster across the whole ARMS sample (ARMS-LT+ARMS-ST) (Pearson's correlation coefficient for SANS -0.445* and for GAF 0.466**) is shown in the middle diagram on the right. The left side of the brain is shown on the left side of the images.

* Significance at the niveau 0.05 2-tailed
** Significance at the niveau 0.01 2-tailed
Abbreviations: ARMS-LT – long-term ARMS; ARMS-ST – short-term ARMS; BPRS – Brief Psychiatric Rating Scale; GAF – Global Assessment of Functioning; HC - healthy controls; SANS – Scale for the Assessment of Negative Symptoms

Supplementary table: Correlation of psychopathology and GMVs.

Cluster	Score	Pearson's correlation coefficient		
		ARMS	ARMS-ST	ARMS-LT
R insula (40 -18 6)	BPRS	-0.210	0.465	-0.231
	APS	-0.107	0.152	0.306
	SANS	-0.376*	0.041	-0.408
	GAF	0.446**	-0.185	0.503
R STG (54 -15 0)	BPRS	-0.307	0.268	-0.269
	APS	-0.214	0.241	-0.189
	SANS	-0.330	-0.368	-0.038
	GAF	0.451**	0.286	0.177
R STG (58 -6 -6)	BPRS	-0.265	0.094	-0.026
	APS	-0.114	0.394	-0.037
	SANS	-0.270	-0.383	0.080
	GAF	0.348*	0.070	0.084
L IPL (-56 -36 27)	BPRS	-0.290	0.192	-0.196
	APS	-0.210	0.058	0.075
	SANS	-0.381*	-0.037	-0.349
	GAF	0.335	-0.495*	0.447
L IPL (-63 -42 42)	BPRS	-0.174	0.086	0.275
	APS	-0.2279	-0.188	0.145
	SANS	-0.099	0.257	0.125
	GAF	0.197	-0.456	0.041
L STG, insula (-46 -31 21)	BPRS	-0.259	0.401	-0.382
	APS	-0.176	0.190	-0.090
	SANS	-0.445*	-0.104	-0.469
	GAF	0.466**	-0.233	0.612*

Correlation of psychopathology and gray matter volume (GMV) in 2 large clusters with less GMV in the ARMS-ST compared to the ARMS-LT.

* Significance level 0.05, 2-tailed

** Significance level 0.01, 2-tailed

Abbreviations: APS - attenuated psychotic symptoms (APS = BPRS9 + BPRS10 + BPRS11 + BPRS15); ARMS-LT – long-term ARMS; ARMS-ST – short-term ARMS; BPRS – Brief Psychiatric Rating Scale: BPRS9 – suspiciousness, BPRS10 – hallucinations, BPRS11 – unusual thought content, BPRS15 – conceptual disorganization; GAF – Global Assessment of Functioning; HC - healthy controls; IPL – inferior parietal lobule; SANS – Scale for the Assessment of Negative Symptoms; STG – superior temporal gyrus

DISCUSSION

Main findings

We used structural MRI to examine individuals at high clinical risk of psychosis. The ARMS subjects were divided into two groups according to different duration of ARMS and probability for transition to psychosis.

In line with previous MRI studies (meta-analyses (Fusar-Poli, et al. 2011; Smieskova, et al. 2010)) we found that both ARMS-ST and ARMS-LT individuals had volumetric abnormalities relative to HCs. These alterations can be interpreted as state-marker risk factors for the disease and are qualitatively similar to those seen in patients with schizophrenia (meta-analyses (Ellison-Wright and Bullmore 2010; Glahn, et al. 2008)). However, we found more prefrontal, insular and middle temporal volumetric reductions in the ARMS-ST group, as compared to the ARMS-LT and HC group, in line with structural deficits in high-risk individuals with later transition to psychosis (meta-analysis (Smieskova, et al. 2010)). By comparing the three groups we found differences of the right insular volume (ARMS-ST, HC, ARMS-LT) what could be associated with some resilience factors. At a symptoms level we showed that negative symptoms correlated negatively and global functioning positively with GMV in specific brain areas within the ARMS subjects.

Vulnerability-associated volumetric differences

Comparing ARMS-ST and HC revealed that vulnerability to psychosis was associated with orbital and middle frontal volumetric reductions. Comparing ARMS-LT and HC revealed more GMV in right insulo-temporal regions. These findings are similar to the published volumetric abnormalities found in ARMS (meta-analysis (Fusar-Poli, et al. 2011)). Compared to ARMS-LT individuals, ARMS-ST showed reduced GMV in the insula bilaterally, corresponding to the reductions seen in ARMS who later transit to psychosis (Borgwardt, et al. 2007a; Pantelis, et al. 2003a; Takahashi, et al. 2009b).

Volumetric differences associated with different transition probability

There was a difference in GMV reduction between ARMS-ST and ARMS-LT. ARMS-ST individuals had decreased GMV in one cluster in the right insula and middle temporal gyrus and the other one in the left inferior parietal lobule and insula as compared to the ARMS-LT group. Such alterations may represent the neurobiological substrate of the different transition probability within the ARMS. In line with this interpretation, these regions were reduced in ARMS with subsequent transition to psychosis as compared to those without transition (Fusar-Poli, et al. 2011; Smieskova, et al. 2010). Furthermore, previous investigations have shown that GVM alterations in some of the above regions may be directly associated with the consistent neurofunctional alterations observed in the ARMS during cognitive tasks (Fusar-Poli, et al. 2010c).

Volumetric differences associated with resilience?

The ARMS-LT subjects showed more right insular volume compared to the ARMS-ST. Interestingly, this GMV increase was detectable not only in the ARMS-LT compared to the ARMS-ST, but as well to the HC group. It is possible that the insular GMV increase may represent activity-related hypertrophy (Draganski, et al. 2006) secondary to neurofunctional activation of insular areas when experiencing psychotic symptoms (O'Daly, et al. 2007). Additionally, we could see here some protective processes. The ARMS individuals differ from each other in the duration and severity of their symptoms, and in their vulnerability to transit to psychosis. Those who are more vulnerable to transit to psychosis might have less resilience factors and vice versa. Some ARMS might have better internal resources, attitudinal approaches and overall functioning (as in unmedicated patients with schizophrenia (Harrow and Jobe 2007)) and can recover from the ARMS subsequently (Simon and Umbricht 2010). Some of the ARMS individuals might be on the ARMS continuum for a longer period of time, like our ARMS-LT subjects still fulfilling the ARMS criteria. Strikingly, right posterior insular abnormalities play an important role in the lack of intero-ceptive insight (Palaniyappan, et al. 2010) and worse functional outcome in schizophrenia (Mohamed, et al. 2009). Thus the awareness of the illness with positive relationship to the recovery (Lysaker, et al. 2007) could be one of the resilience factors associated with insular volume increase (Lappin, et al. 2007).

Clinical implications

The mean duration of the ARMS was 4.5 years in the ARMS-LT group; the probability that any of these subjects will develop psychosis in the future is low (Cannon, et al. 2008; Riecher-Rössler, et al. 2009). In the ARMS-ST subjects, we expect a transition rate of approximately 20-40% (Riecher-Rössler, et al. 2009) in the next one to two years. This allows the investigation of vulnerability and higher transition probability associated changes in brain activation in the ARMS-ST compared to the HC. Interestingly, our ARMS-LT did not differ from the ARMS-ST in age. This could be because of small sample sizes and needs further investigation. On the other hand, the differences between ARMS-ST and ARMS-LT are not solely attributable to the difference in age between those groups.

The structural abnormalities we found were not directly attributable to antipsychotic treatment, as all of the ARMS-ST individuals were antipsychotic-naïve and only 2 ARMS-LT individuals had antipsychotic treatment at the time of scanning. The influence of antipsychotics on the brain function is not entirely clear, however antipsychotics may affect GMV (Ho, et al. 2011a). Furthermore, both individuals were treated with atypical neuroleptics in very low doses. Consequently we argue that the volumetric differences between these two groups reflect both disrupted brain structure and protective processes, as discussed above. It remains unknown, whether structural abnormalities are reversible or compensatory in their nature. Some recent studies reported reversibility of prodromal symptoms, especially in adolescent high risk group (Simon and Umbricht 2010).

Correlation with clinical outcomes

We proved partially our second hypothesis of correlation between volumetric differences and psychotic symptoms. Negative symptoms correlated negatively with the GMV reduction in the insula and left parietal regions within our whole ARMS population. However, positive symptoms did not correlate with the GMV changes at all. Previous studies have found negative correlations between positive symptoms and GMV (Crespo-Facorro, et al. 2000; Pressler, et al. 2005) as well as no correlation (Crespo-Facorro, et al. 2010) in schizophrenia.

As opposed to that, reduced GMV in the bilateral insula and in the right superior and middle temporal gyrus positively correlated with functional decline within the whole ARMS group. This is in line with a previous study indicating that the duration of prodromal symptoms predicts the longitudinal GAF scores in subjects with an ARMS (Fusar-Poli, et al. 2009b).

Limitations

Some limitations of this study should be considered. Firstly, although the ARMS-ST group has a 20-40% probability of transition to psychosis, there is a high false positive probability of approximately 60-80%. That could be the reason, why we found the differences with relatively low significance in the group comparison. These between group differences could be more pronounced in the pure transition group. Secondly, we found no significant correlation between clinical and structural measures in our ARMS-ST and ARMS-LT subgroups, only within the whole ARMS group. This could be caused by the small sample sizes. However, we examined especially those regions with relative structural differences between the groups. Thirdly, a large portion of the ARMS-ST individuals could become ARMS-LT in several months, and with the aim to investigate longitudinal differences in the same individuals, we should scan them then again in 4.5 years. Fourthly, the use of VBM methodology brings problems of brain registration and the size of the smoothing kernel. This is relevant especially when relatively small differences are expected, as it is the case in ARMS individuals. The exact meaning of volumetric abnormalities (exaggerated dendritic pruning, impaired myelination, apoptosis or neuropil changes) is not entirely clear. All the same, this technique allows the comparison of the entire brain volumes at the single voxel level, and we used the improved segmentation and normalization SPM8 protocols (Yassa and Stark 2009) in our analyses.

Conclusions

Structural alterations in subjects at high clinical risk for psychosis are associated with negative symptoms and impairment in global functioning. Specific gray matter volume abnormalities within the ARMS may distinguish different transition probabilities and resilience factors. In particular, volume loss in the insula is associated with a higher risk for transition to psychosis.

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CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest.

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Different duration of at-risk mental state associated with neurofunctional abnormalities.
A multimodal imaging study

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ABSTRACT

Objectives: Neurofunctional alterations are correlates of vulnerability to psychosis, as well as of the disorder itself. How these abnormalities relate to different probabilities for later transition to psychosis is unclear. We investigated vulnerability- versus disease-related versus resilience biomarkers of psychosis during working memory processing in individuals with an at-risk mental state (ARMS).

Experimental design: Patients with 'first-episode psychosis' (FEP, n=21), short-term ARMS (ARMS-ST, n=17), long-term ARMS (ARMS-LT, n=16), and healthy controls (HC, n=20) were investigated with an n-back working memory task. We examined functional (fMRI) and structural magnetic resonance imaging (sMRI) data in conjunction using Biological Parametric Mapping (BPM) toolbox.

Principal observations: There were no differences in accuracy, but the FEP and the ARMS-ST group had longer reaction times compared to the HC and the ARMS-LT group. With the 2-back>0-back contrast we found reduced functional activation in ARMS-ST and FEP compared to the HC group in parietal and middle frontal regions. Relative to ARMS-LT individuals, FEP patients showed decreased activation in the bilateral inferior frontal gyrus and insula, and in the left prefrontal cortex. Compared to the ARMS-LT, the ARMS-ST subjects showed reduced activation in the right inferior frontal gyrus and insula. Reduced insular and prefrontal activation was associated with gray matter volume reduction in the same area in the ARMS-LT group.

Conclusions: These findings suggest that vulnerability to psychosis was associated with neurofunctional alterations in fronto-temporo-parietal networks in a working memory task. Neurofunctional differences within the ARMS were related to different duration of the prodromal state and resilience factors.

INTRODUCTION

Neurofunctional alterations are a leading feature of psychosis. To date, it is not clear to what extent these abnormalities correlate with vulnerability to psychosis or pathology of the disorder itself. However, for the understanding of their pathogeneses it is important to clarify their onset and time course of the dynamic neurobiological processes underlying the transition from a high-risk state to manifest psychosis.

Working memory (WM) impairment is one of the most pronounced cognitive features found in schizophrenia (Callicott et al., 2003b; Cannon et al., 2005; Forbes et al., 2009; Glahn et al., 2005; Jansma et al., 2004; Johnson et al., 2006; Manoach et al., 2000; Menon et al., 2001; Schneider et al., 2007). Impairments in the WM network activation depend on the individual performance (Ettinger et al., 2011), higher performing patients with schizophrenia showed hyper-activation and lower performing patients showed hypo-activation what was explained using the compensation model of activation (Sanz et al., 2009). However, the relation of physiological and clinical variables (positive, negative symptoms) is complicated by the multidimensional nature of psychotic symptoms. Recent advances in psychiatric research indicate that neurocognitive deficits are also evident in subjects with an at-risk mental state (ARMS) (Eastvold et al., 2007; Pflueger et al., 2007; Simon et al., 2007; Smith et al., 2006) and in non-affected first-degree relatives (Karch et al., 2009; Karlsgodt et al., 2007; Lee et al., 2010a; MacDonald et al., 2009; Meda et al., 2008; Spence et al., 2000).

The ARMS is defined according to the PACE (Personal Assessment and Crisis Evaluation Clinic, Melbourne) criteria and requires individuals to present attenuated positive psychotic or brief limited intermittent symptoms that do not reach full psychosis threshold (Riecher-Rössler et al., 2007; Riecher-Rössler et al., 2009; Yung et al., 2004) or functional decline. These psychopathological symptoms are often associated with negative (Lencz et al., 2004; Riecher-Rössler et al., 2009) symptoms, subtle cognitive deficits (Brewer et al., 2006; Riecher-Rössler et al., 2009) and include deficits in working memory function (Broome et al., 2010; Simon et al., 2007). Those with the ARMS have a 20–40% probability of developing the psychosis (Riecher-Rössler et al., 2007; Riecher-Rössler et al., 2009; Yung et al., 1998). Furthermore, neurofunctional deficits may be associated with transition to psychosis and thus can be seen as vulnerability markers for developing schizophrenia (Morey et al., 2005; Riecher-Rössler et al., 2009).

Over the past decade, structural (sMRI) and functional magnetic resonance imaging (fMRI) methods have been extensively employed to identify the anatomical and neurofunctional alterations in the pre-psychotic phases. In subjects at high-risk for psychosis, MRI studies showed structural abnormalities (Borgwardt et al., 2007a; Borgwardt et al., 2008; Borgwardt et al., 2006; Borgwardt et al., 2007b; Koutsouleris et al., 2009; Meisenzahl et al., 2008; Pantelis et al., 2003; Witthaus et al., 2009) and neurofunctional deficits in the frontal and temporal task-related networks (Allen et al., 2010; Fusar-Poli et al., 2007a), especially during working memory tasks (Broome et al., 2010; Broome et al., 2009; Pauly et al., 2010). Such alterations are not only attributable to the effects of illness or treatment and may represent markers of vulnerability to psychosis (Smieskova et al., 2010).

Since 1999, the Early Detection of Psychosis Clinic (FEPSY) in Basel recruited and followed up the ARMS individuals over up to 7 years (Riecher-Rössler et al., 2009). Importantly, 19 of those 21 ARMS

individuals who made transition, transit in the first two years after their ascertainment. Afterwards, only 2 out of 53 included ARMS individuals made transition to psychosis (Riecher-Rössler et al., 2009) representing a reduced transition probability. Similarly, the vast majority of transitions occur in the first two years (estimated hazard ratio 0.58) and significantly dropped over time (estimated hazard ratio 0.07) (Yung et al., 2007). In the present study, we therefore investigated the ARMS individuals with a short or long duration of the ARMS. All these individuals fulfil the ARMS criteria (similar to the PACE criteria) at the time of scan. In the first group (short-term ARMS, ARMS-ST), the scan was done at the time of ascertainment of the ARMS (within 3 months on average). In the second group (long-term ARMS, ARMS-LT), the scan was done after 2 years, on average 4.5 years of follow-up with no transition to psychosis. At the time of the scan in the latter group, the assessment of the ARMS was repeated and PACE criteria were still met. We thus investigated two ARMS subgroups both representing vulnerability to psychosis with different probabilities of later transition to psychosis. It is important to emphasize that also ARMS-LT group continue to meet ARMS criteria at the time of scan. This group is therefore clearly on the risk continuum to develop psychosis, but according to the published data has lower probability to develop subsequent psychosis than ARMS-ST. In this context, we aimed to examine the neurofunctional brain abnormalities associated with higher vs. lower probability of developing psychosis. This could improve our understanding of the neurofunctional changes in the mental state in early stages in the context of clinical staging model (McGorry et al., 2009).

Until now, there is a small number of fMRI studies in people with an ARMS (Broome et al., 2010; Broome et al., 2009; Fusar-Poli et al., 2010a; Fusar-Poli et al., 2010b) investigating neurofunctional abnormalities while performing a working memory task. Expanding the previous study (Broome et al., 2009), here we investigated an ARMS-LT group with a lower probability of developing psychosis compared to the ARMS-ST group (Yung et al., 2007).

Additionally, we focused on functional and structural differences between individuals with vulnerability to develop psychosis and already psychotic individuals (patients with first-episode psychosis, FEP). Thus, we specifically wanted to test vulnerability- versus disease-related versus resilience biomarkers of psychosis.

On the basis of previous findings (Broome et al., 2009), we tested the following hypotheses:

1. The WM-specific activation would be diminished in parallel with the clinical status (ARMS-LT<ARMS-ST<FEP) compared to the healthy control (HC) group.
2. The ARMS-ST group would show more functional deficits associated with volumetric abnormalities compared to the ARMS-LT group.

MATERIALS AND METHODS

Subjects

MRI data were collected as part of a research program on early detection of psychosis that is described in detail elsewhere (Riecher-Rössler et al., 2006). Briefly, we recruited subjects with an ARMS and patients experiencing a FEP in our specialized clinic for the early detection of psychosis at the Psychiatric Outpatient Department, Psychiatric University Clinics Basel, Switzerland.

The entire group of individuals with an ARMS (ARMS-ST and ARMS-LT; n=33) corresponds to the criteria by Yung (Yung et al., 1998) employed in previous MRI studies (Borgwardt et al., 2007a; Borgwardt et al., 2007b; Pantelis et al., 2003; Sun et al., 2009; Takahashi et al., 2009a; Takahashi et al., 2009b; Velakoulis et al., 2006; Walterfang et al., 2008; Wood et al., 2003; Wood et al., 2005). All the ARMS individuals were assessed at the time of MRI scan. Inclusion thus required one or more of the following a) "attenuated" psychotic symptoms b) brief limited intermittent psychotic symptoms (BLIPS) or c) a first degree relative with a psychotic disorder plus at least two indicators of a clinical change, such as a marked decline in social or occupational functioning.

We divided the ARMS individuals into two subgroups depending on the duration of the ARMS status since its first presentation. The ARMS-ST group had the MRI scan as soon as practicable, on average within 3 months after ascertainment. The ARMS-LT group comprise of individuals who did not convert to psychosis over a longer follow up period of on average 4.5 years after first ascertainment. The mean duration of follow up of ARMS-ST subjects was 2.88 months (SD=5.24), with one individual who developed psychosis. The mean follow up time since presentation in ARMS-LT subgroup was 55.44 months (SD=24.72). The range for the follow-up time since presentation was 0-17 months in the ARMS-ST group and 27-96 months in the ARMS-LT group. At time of scanning all the ARMS-ST and ARMS-LT individuals still fulfilled the criteria by Yung et al. for ARMS (Riecher-Rössler et al., 2008; Yung et al., 1998) but had different probabilities of developing psychosis (Cannon et al., 2008; Riecher-Rössler et al., 2009; Yung et al., 2008).

During follow-up, the ARMS-ST and ARMS-LT subjects received psychiatric case management without any antipsychotic treatment. All the ARMS individuals (from both groups) were antipsychotic-naïve. However, the general practitioners had treated the minority of them: one subject was at the time of scanning antipsychotic-free (olanzapine 2.5 mg/day for 9 months; 4 months before the scan) and two ARMS-LT subjects were currently medicated (1 zuclopenthixol 3x40 mg/day, and 1 aripiprazole 5mg/day, for unknown period prescribed for treatment of negative symptoms). Furthermore, 8 of ARMS-LT and 6 of ARMS-ST were receiving antidepressants at the time of the MRI scan. The small amount of individuals receiving antidepressant precluded analysis of putative neurofunctional effect of antidepressants (Fusar-Poli et al., 2007b).

The FEP patients (n=21) were defined as subjects who met the operational criteria for ‘first-episode psychosis’(Breitborde, 2009). Inclusion required scores of 4 or above on the hallucination item or 5 or above on the unusual thought content, suspiciousness or conceptual disorganization items of the BPRS (Yung et al., 1998). The symptoms must have occurred at least several times a week and persisted for

more than one week. Most of our FEP patients were not receiving medication (7 of them antipsychotic-naïve, 6 antipsychotic-free) at time of scanning. Eight FEP patients were receiving antipsychotics at the time of scanning for approximately 2 months (5 quetiapine and 2 paliperidone for less than 6 months, 1 olanzapine for less than 2 years).

We assessed subjects using the 'Basel Screening Instrument for Psychosis' (BSIP) (Riecher-Rössler et al., 2008; Riecher-Rössler et al., 2007), the Brief Psychiatric Rating Scale (BPRS)(Lukoff et al., 1986), the Scale for the Assessment of Negative Symptoms (SANS)(Andreasen, 1989) and the Global Assessment of Functioning (GAF). The BSIP evaluates 'prodromal' symptoms (defined according to the Diagnosis and Statistical Manual of Mental Disorder, DSM-III-R) occurring in the last 5 years; nonspecific 'prodromal' signs (Riecher-Rössler et al., 2007) in the last 2 years; previous or current psychotic symptoms, psychosocial functioning over the last 5 years, substance dependency; and psychotic disorders among first and second degree relatives (Riecher-Rössler et al., 2008) . We obtained current and previous psychotropic medication, alcohol, nicotine, cannabis, and other illegal drug consumption using a semi-structured interview adapted from Early Psychosis Prevention and Intervention Centre (EPPIC) Drug and Alcohol Assessment Schedule (www.eppic.org.au).

We applied the following exclusion criteria to both these groups: history of previous psychotic disorder; psychotic symptomatology secondary to an 'organic' disorder; substance abuse according to ICD-10 research criteria; psychotic symptomatology associated with an affective psychosis or a borderline personality disorder; age under 18 years; inadequate knowledge of the German language; and IQ (Lehrl et al., 1995) less than 70.

We recruited healthy volunteers (HC, n=20) from the same geographical area as the other groups. All subjects were representative of the local population of individuals presenting with an ARMS or FEP in terms of age, gender, handedness, and alcohol and cannabis consumption. These individuals had no current psychiatric disorder, no history of psychiatric illness, head trauma, neurological illness, serious medical or surgical illness, substance abuse, and no family history of any psychiatric disorder as assessed by an experienced psychiatrist in a detailed clinical semi-structured interview. All participants provided written informed consent, and the study had research ethics committee permission.

Magnetic resonance image acquisition

Functional MRI

We acquired the n-back task elicited images on a 3 T scanner (Siemens Magnetom Verio, Siemens Healthcare, Erlangen, Germany) using an echo planar sequence with a repetition time (TR) of 2.5 s, echo time (TE) of 28 ms, matrix 76x76, 126 volumes and 38 slices with 0.5 mm interslice gap, providing a resolution of 3x3x3 mm^3, and a field of view (FOV) 228x228 cm^2. With an inter-stimulus interval of 2 seconds, all subjects saw the series of black letters on the white background in a prismatic mirror. Each stimulus was presented for 1 second. The size of the letters was 8 cm projected on the screen at the end of the scanner. All participants with myopia had the possibility to use plastic glasses and the readability was controlled always before the experiment started. During a baseline (0-back) condition, subjects were

required to press the button with the right hand when the letter „X" appeared. During 1-back and 2-back conditions, participants were instructed to press the button if the currently presented letter was the same as that presented 1 (1-back condition) or 2 (2-back condition) trials beforehand. The three conditions were presented in 10 alternating 30 s blocks (2 x 1-back, 3 x 2-back and 5 x 0-back) matched for the number of target letters per block (i.e. 2 or 3), in a pseudo-random order. The reaction times and response accuracy were recorded on-line.

Structural MRI

For anatomical imaging a 3D T1-weighted MPRAGE sequence was applied with 1x1x1 mm^3 isotropic spatial resolution and with inversion time of 1000 ms, TR of 2 s and TE of 3.4 ms. All scans were screened for gross radiological abnormalities by an experienced neuroradiologist. Five individuals were not included to the analyses due to arachnoidal cysts, cavernom, cerebellar atrophy and T2 hyperintensities (Borgwardt et al., 2006).

Image analysis

We analyzed functional MRI data using the Statistical Parametric Mapping software package (SPM8; Wellcome Department of Cognitive Neurology, London, United Kingdom). All volumes were realigned to the first volume, corrected for motion artefacts, mean adjusted by proportional scaling, normalized into standard stereotactic space (template provided by the Montreal Neurological Institute), and smoothed using a 8 mm full-width-at half-maximum (FWHM) Gaussian kernel. After exclusion of error trials, we convolved the onset times for each trial in seconds with a canonical hemodynamic response function.

We pre-processed all structural images with the Voxel-Based Morphometry (VBM8) toolbox (http://dbm.neuro.uni-jena.de/vbm8/) implemented in SPM8. It utilizes New Segmentation and DARTEL methods in SPM8. We modulated the segmented tissue maps of gray matter (GM) with the Jacobian determinants from the spatial normalization to correct for volume changes. We chose the option 'modulation of non-linear effects only', which equals the use of default modulation (of both affine and non-linear effects) and globally scaling data according to the inverse scaling factor due to affine normalization. Finally, we smoothed the modulated GM images with an 8-mm FWHM Gaussian kernel.

Integration of multimodal imaging data

We chose the multimodal integrative image analysis to determine if brain abnormalities in working memory were associated with volumetric abnormalities in ARMS-ST, ARMS-LT and FEP individuals. We used Biological Parametric Mapping (BPM) (Casanova et al., 2007) toolbox, developed in Matlab and visualized our results in SPM8. Using 1st level 2-back>0-back contrast images, we provided BPM Analysis of covariance (ANCOVA) analyses with all 4 groups in one model. The fMRI data were the primary modality and the corresponding VBM data the imaging covariates. We evaluated the impact of the group structural differences on the fMRI data on a voxel-wise basis with gray matter volume (GMV) as a regressor. To account for age- and sex-specific associations (Elsabagh et al., 2009) we used age and gender as covariates in the ANCOVA model. We have run the integrative analyses twice, one with and one without GMV as covariate to find the regions where the group differences were lost due to this covariation. We chose 2-back>0-back contrasts as attention-independent modality with higher load level to search differences across groups. To specify the WM-associated network of activation, we used the 'main-effect of n-back task' (full-factorial model; $p<0.001$, FWE-corrected) as a mask for 2nd level analyses. The correlation between the blood oxygen level-dependent (BOLD) signal and GMV was calculated on a voxel-by-voxel basis with the BPM correlation model (Casanova et al., 2007).

Statistical significance in all analyses (VBM, fMRI and BPM) was assessed at the cluster-level using the non-stationary random field theory (Hayasaka et al., 2004). The first step of this cluster-level inference strategy consisted of identifying spatially contiguous voxels at a threshold of $p<0.01$, uncorrected (cluster-forming threshold) (Petersson et al., 1999). Finally, a family-wise error (FWE) corrected cluster-extent threshold of $p<0.05$ was defined in order to infer statistical significance. To provide sufficient details about the present study, we followed the guidelines for reporting an fMRI study (Poldrack et al., 2008).

To label the regions of brain activation MNI coordinates were transformed into Talairach space (www.ebire.org/hcnlab/cortical-mapping; Talairach Daemon software; (Mai JK, 2008)).

Statistical analysis of demographic data

We examined clinical and socio-demographic differences between groups using one-way analysis of variance (ANOVA), F-test, or chi-square test (Table 1). For post-hoc analyses we used the least-significant difference (LSD) correction. Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS 16.0).

RESULTS

Clinical and demographic characteristics of the sample

There were no significant differences among our groups with respect to age (P=0.177), gender (P=0.245), handedness (P=0.638), IQ (P=0.166), current alcohol (P=0.247) and cannabis (P=0.489) consumption. There were significant between group differences in positive and negative symptoms, and in global functioning over all our groups. The FEP group had more positive symptoms than ARMS-ST (P=0.006), ARMS-LT (P<0.001) and HC (P<0.001) groups. The ARMS-ST group showed a higher BPRS (P=0.018) and SANS (P=0.015) and a lower GAF (P<0.0001) score compared to the ARMS-LT (Table 1).

N-back task performance

There was no difference in the accuracy in any of conditions. Reaction times were significantly longer in the FEP compared to the HC and ARMS-LT groups and in the ARMS-ST compared to the HC and ARMS-LT groups (Supplementary table 1).

Table 1: Demographic and clinical characteristics.

Characteristic	FEP (n=21)	ARMS-ST (n=17)	ARMS-LT (n=16)	HC (n=20)	Statistics	
Gender M/F, (male)	16/5 (76.2%)	13/4 (76.5%)	11/5 (68.8%)	10/10 (50.0%)	P=0.245	$\chi2$=4.154
Mean age in yrs (SD)	28.57 (7.2)	25.24 (6.3)	25.06 (2.3)	26.50 (4.0)	P=0.177	F=1.691
Handedness (left)	2 (9.5%)	0	1 (6.2%)	1 (5%)	P=0.638	$\chi2$=1.697
MWT-B_IQ	107 (14.2)	112 (14.1)	106 (12.4)	114 (9.8)	P=0.166	F=1.749
Years of education (SD)	13.35 (3.14)	13.80 (3.62)	13.88 (2.38)	16.38 (2.96)	P=0.012	F=3.940
Post-hoc	FEP<HC: P=0.003	ARMS-ST<HC: P=0.016	ARMS-LT<HC: P=0.017			
Time since presentation (yrs) (SD)	2.90 (2.84)	0.24 (0.437)	4.62 (2.06)	0	P<0.0001	F=18.135
BPRS total score (SD)	49.20 (15.02)	40.30 (8.33)	32.31 (6.27)	24.50 (1.15)	P<0.0001	F=24.783
Post-hoc	FEP>HC: P<0.0001	ARMS-ST>HC: P<0.0001	ARMS-LT>HC: P=0.015			
	FEP>ARMS-LT: P<0.001	ARMS-ST<FEP: P=0.006	ARMS-LT <ARMS-ST: P=0.018			
SANS total score (SD)	28.05 (16.20)	21.88 (13.04)	10.53 (15.20)	0	P<0.0001	F=18.132
Post-hoc	FEP>HC: P<0.0001	ARMS-ST>HC: P<0.0001	ARMS-LT>HC: P=0.018			
	FEP>ARMS-LT: P<0.001	ARMS-ST>ARMS-LT: P=0.015				
GAF (SD)	56.50 (14.32)	58.94 (12.63)	75.33 (14.86)	88.50 (4.44)	P<0.0001	F=29.707
Post-hoc	FEP<HC: P<0.0001	ARMS-ST<HC: P<0.0001	ARMS-LT<HC: P=0.002			
	FEP<ARMS-LT: P<0.0001	ARMS-ST<ARMS-LT: P<0.0001				
Antipsychotics at MRI scan	8 (38%)	0 (0%)	2 (12.5%)	0 (0%)	P=0.001	$\chi2$= 16.653
Antidepressants at MRI scan	8 (38.1%)	6 (35.3%)	8 (50.0%)	0 (0%)	P=0.006	$\chi2$=12.564
Smoking cigarettes/day (SD)	13.33 (13.17)	8.15 (10.19)	8.94 (11.86)	2.85 (5.92)	P=0.024	F=3.345
Post-hoc	FEP>HC: P=0.002					
Alcohol currently					P=0.274	$\chi2$=7.538
no	4 (19%)	2 (11.8%)	2 (12.5%)	1 (5.0%)		
moderate	10 (47.6%)	6 (35.3%)	8 (50.0%)	15 (75.0%)		
s.t. drunkenness	7 (33.3%)	9 (52.9%)	6 (37.5%)	4 (20.0%)		
Cannabis currently	7 (35.0%)	7 (43.8%)	5 (31.2%)	4 (20%)	P=0.489	$\chi2$=2.428

Abbreviations: ARMS-ST – short-term ARMS; ARMS-LT – long-term ARMS; BPRS – Brief Psychiatric Rating Scale; GAF – Global Assessment of Functioning; HC - healthy controls; MWT-B - multiple choice vocabulary test (Mehrfachwahl-Wortschatz-Test Form B), FEP - 'first-episode psychosis'; SANS – Scale for the Assessment of Negative Symptoms

Supplementary table1: Behavioural data during n-back task.

Characteristic	FEP (n=21)	ARMS-ST (n=17)	ARMS-LT (n=16)	HC (n=20)	Statistics	
n-back errors (SD)	8.76 (9.2)	5.59 (6.2)	11.69 (11.7)	5.5 (7.6)	P=0.133	F=1.926
0-back errors (SD)	3.57 (5.0)	1.82 (3.5)	5.31 (5.8)	2.4 (4.0)	P=0.149	F=1.836
1-back errors (SD)	1.81 (2.0)	1.06 (1.6)	2.06 (2.5)	1.05 (1.6)	P=0.283	F=1.294
2-back errors (SD)	3.38 (3.2)	2.71 (2.2)	4.38 (4.0)	2.05 (2.4)	P=0.129	F=1.953
0-back t_R (SD)	760.6 (84.4)	709.8 (88.9)	659 (107.0)	640.4 105.9)	P=0.002	F=5.474
1-back t_R (SD)	770.4 (89.5)	732.5 (96.8)	690.9 (129.5)	690.7 (102.1)	P=0.076	F=2.400
2-back t_R (SD)	809.2 (71.5)	788.5 (67.4)	727.6 (88.8)	730 (107.3)	P=0.012	F=3.946

Using the least-significant difference (LSD) post-hoc correction we found significantly longer reaction times only in the FEP group compared to the HC and to the ARMS-LT.
Abbreviations: ARMS-ST – short-term ARMS; ARMS-LT – long-term ARMS; FEP - 'first-episode psychosis', HC - healthy controls; n-back errors – number of errors during n-back task, t_R - reaction time

Supplementary table 2: Group differences in gray matter volume

Group comparisons	$p_{FWE-corr}$ clustel level	Voxels	MNI x y z	T at voxel level	Side	Brain region
FEP<HC	0.0001	6817	-10 -87 -5 4 -66 7 -20 -91 -3	5.13	L, R	Lingual gyrus and PCG (BA 17, 30)
	0.0001	2349	38 50 -20 38 40 -21 28 44 -15	4.14	R	MFG and SFG (BA 11)
	0.0001	3414	0 42 -2 3 32 -2 3 16 -11	3.89	L, R	ACG (BA 32, 24, 25)
	0.001	1609	27 -48 -14 32 -34 -9 40 -61 -17	3.75	R	Fusiform G and hippocampus (BA 37)
	0.0001	4520	-40 -49 -29 -22 -42 -18 -33 -64 -63		L	Anterior lobe, culmen
	0.0001	2168	52 -12 40 40 -6 64 60 -7 33	3.68	R	PrecentralG and MFG (BA 4, 6)
	0.0001	2407	-39 51 -20 -44 41 12	3.49	L	MFG and IFG (BA11, 46)
	0.004	1309	45 -66 -57	3.18	R	Cerebellum
FEP<ARMS-LT	0.005	1296	-56 -45 27 -44 -46 25 -45 -33 22	4.05	L	IPL extending into STG and insula (BA 40, 13)
	0.0001	3203	60 -4 -8 32 -28 21 48 -21 6	3.78	R	MTG extending into insula and STG (BA 21, 13)
	0.001	1589	-24 -39 -39 -38 -49 -29 -22 -36 -24	3.50	L	Cerebellum, culmen
FEP<ARMS-ST	0.002	1487	50 15 1 44 16 15 51 15 30	4.89	R	IFG and MFG (BA 47, 44, 9)
	0.002	1485	-38 27 9 -42 15 -3 -54 15 -5	4.35	L	IFG (BA 45, 47, 22)
	0.011	1137	57 -33 37 60 -42 49 60 -27 33	3.62	R	IPL (BA 40)
	0.025	984	-38 -88 -21 -28 -94 -21 -48 -79 -17	3.45	L	IOG, Fusiform G, MOG (BA 18, 19)
ARMS-ST<HC	0.010	1157	16 40 -6 3 24 -18 -9 26 -12	3.52	R, L	Paracingulate G, ACG (BA 32, 25, 11)
	0.017	1055	-34 45 24 -44 44 12 -27 29 29	3.44	L	MFG extending into IFG (BA 10, 9, 46)
ARMS-LT<HC	0.001	1567	-6 33 21 -2 44 -2 -2 36 -12	4.66	L	ACG, paracingulate G (BA 24, 32, 11)
	0.027	966	60 -7 22 45 -7 25	3.63	R	Precentral gyrus (BA 4, 6)
ARMS-LT>HC	0.033	930	33 -28 22 33 -28 9	3.46	R	Insula and transverse TG (BA 41)
ARMS-ST<ARMS-LT	0.018	1039	58 -4 -8 42 -19 6 56 -16 0	3.38	R	MTG extending into insula and STG (BA 21, 13, 22)

There were no significant differences in contrasts: FEP>HC, ARMS-ST>HC, ARMS-ST>ARMS-LT, FEP>ARMS-ST, FEP>ARMS-LT.

Supplementary table 2 abbreviations:
ACG - anterior cingulate gyrus; ARMS-ST – short-term at risk mental state; ARMS-LT – long-term ARMS; BA - Brodman area; FEP – firt episode of psychosis; G - gyrus; HC - healthy controls; IFG - inferior frontal gyrus; IOG - inferior occipital gyrus; IPL - inferior parietal lobule; MFG - middle frontal gyrus; MOG - middle occipital gyrus, MOL - middle occipital lobe; MTG - middle temporal gyrus; PCG - posterior cingulate gyrus; SFG - superior frontal gyrus; TG – temporal gyrus.

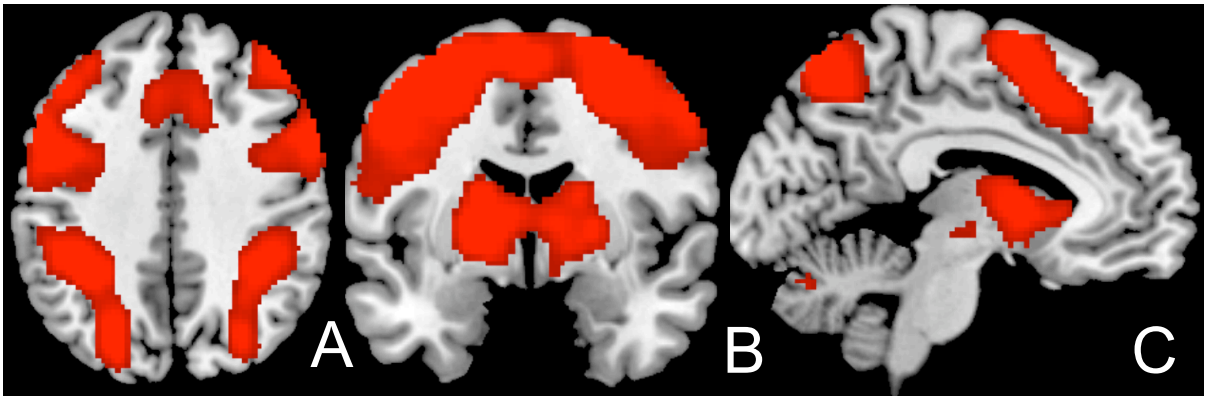
Gray matter volumes (VBM results)

The FEP group showed reduced GMV in the anterior cingulo-prefrontal, hippocampal, and occipito-cerebellar regions, compared to HC group (P<0.01). Compared to the ARMS-LT, the FEP group had temporo-insular volumetric reductions (P<0.005). Compared to the ARMS-ST group, FEP had reduced volumes in the fronto-parietal and occipital regions (P<0.05). Both the ARMS-ST and ARMS-LT groups had anterior cingular and frontal volumetric reductions compared to the HC group (P<0.05). There was more GMV in insula in the ARMS-LT group compared to the HC group. The ARMS-ST showed volumetric reductions in the temporal gyrus extending into insula, compared to the ARMS-LT group (Supplementary table 2).

N-back fMRI results

Main effect of task

The main effect of task (2-back>0-back) in all 74 subjects delineates the network of activated areas independent of group. We used this task effect as a mask to constrain subsequent group analyses to a working memory network (Supplementary figure).



Supplementary Figure: The main effect of 2-back>0-back brain activation across all 74 included subjects (FEP, ARMS-ST, ARMS-LT, and HC).
The regional brain activation (P<0.001) was found in a network of areas that included the left middle and superior frontal gyrus (subsidiary focus of activation x=-32 y=0 z=54 and -2 6 60, voxels=23339), the bilateral superior and inferior parietal lobule (peak area of activation -10 -66 56, voxels=10128 and subsidiary focus of activation -56 -44 22), the bilateral middle temporal gyrus (peak area of activation -30 -58 30, voxels=54 and subsidiary focus of activation 56 -54 -12), the right thalamus (10 -22 16), the left lentiform nucleus and putamen (-30 -20 -6), and the bilateral cerebellum (peak area of activation 32 -60 -30, voxels=202). The left side of the brain is shown on the left side of the images, the axial, coronal and sagittal views are labelled with A, B and C respectively.

Integrative image analysis using functional and structural imaging modalities

Vulnerability-associated abnormalities of developing psychosis

The ARMS-ST group activated less than the HC group in the bilateral superior and right inferior parietal lobule (P<0.0001), and in the left superior frontal gyrus (P<0.05; Table 2, Figure 1). The ARMS-LT group showed no significant functional differences compared to the HC group.

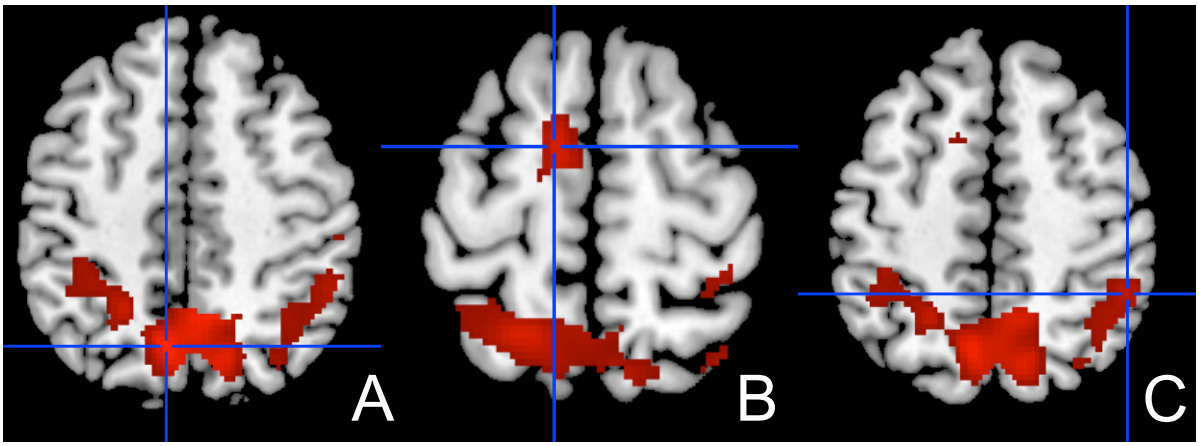


Figure 1: Vulnerability-associated group differences in activation.
The crosses show the peak area of different activation between the ARMS-ST and the HC groups. Clusters in the bilateral superior parietal lobule (x=-8; y=-64; z=48; voxels=2738, panel A), in the left superior frontal gyrus (-12 0 62; voxels=312, panel B), and in the right inferior and superior parietal lobule (48 -44 52; voxels=741, panel C) reflect decreased regional brain activation in the ARMS-ST as compared to the HC group during the 2-back>0-back task (P<0.05). Covarying for GMV had no effect on these results. The left side of the brain is shown on the left side of the images.

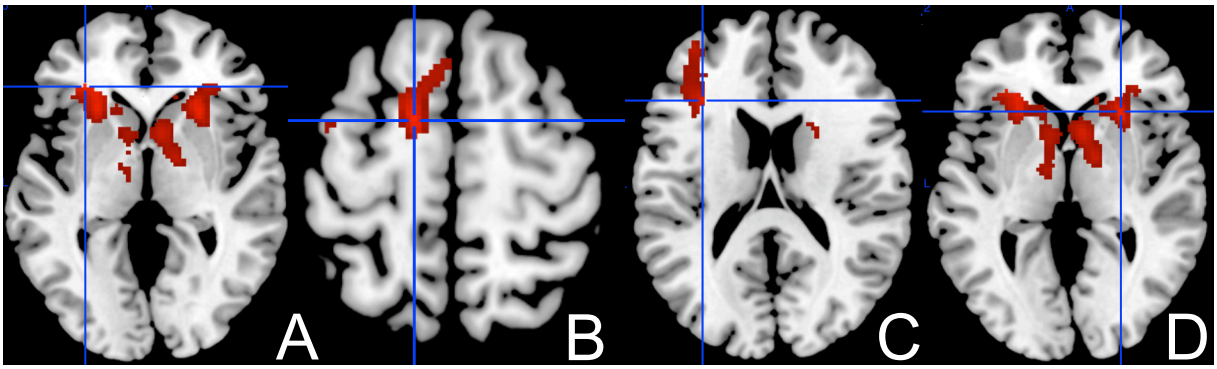


Figure 2: Psychosis-associated group differences in activation.
The crosses show the peak area of different activation between the FEP and the ARMS-LT groups. Clusters in the left inferior and orbital frontal gyrus and insula (x=-32; y=34; z=0; voxels=1568, panel A), in the left superior frontal gyrus (-14 0 60; voxels=402, panel B), and in the left inferior and middle frontal gyrus (-34 26 18; voxels=689, panel C) reflect decreased regional brain activation in the FEP as compared to the ARMS-LT group during the 2-back>0-back task (P<0.01). After covarying for GMV the cluster in the right inferior frontal gyrus and insula (26 22 2; voxels=406, panel D) became significant. The left side of the brain is shown on the left side of the images.

Psychosis-associated abnormalities

The FEP group showed less brain activation in the bilateral precuneus extending into superior parietal lobule and in the left superior and middle frontal gyrus (P<0.0001) compared to the HC group. Compared to the ARMS-LT, the FEP group showed reduced activation in the bilateral inferior frontal gyrus and insula, in the left superior frontal gyrus, and in the middle frontal gyrus (P<0.01; Table 2, Figure 2). Correlation analyses in the FEP individuals under BPM confirmed a negative interaction between BOLD response and GMV in right precuneus (36 -72 44; P=0.032). There were no significant differences in brain activation in the FEP group compared to the ARMS-ST group.

Neurofunctional abnormalities associated with high probability to develop psychosis

Compared to the ARMS-LT, the ARMS-ST subjects showed reduced activation in the right inferior frontal gyrus extending into insula (p<0.05) and in the left superior frontal gyrus, insula and bilateral precuneus (p<0.1) (Figure 3, Table 2). There was a positive correlation between BOLD response and GMV in left precuneus (-28 -72 24; P=0.003) in the ARMS-ST group; and in right insula (42 -18 -10; P=0.015), left inferior frontal gyrus (-32 32 -18; P=0.002), and in right lingual gyrus (32 -72 -12; P=0.0001) in ARMS-LT group.

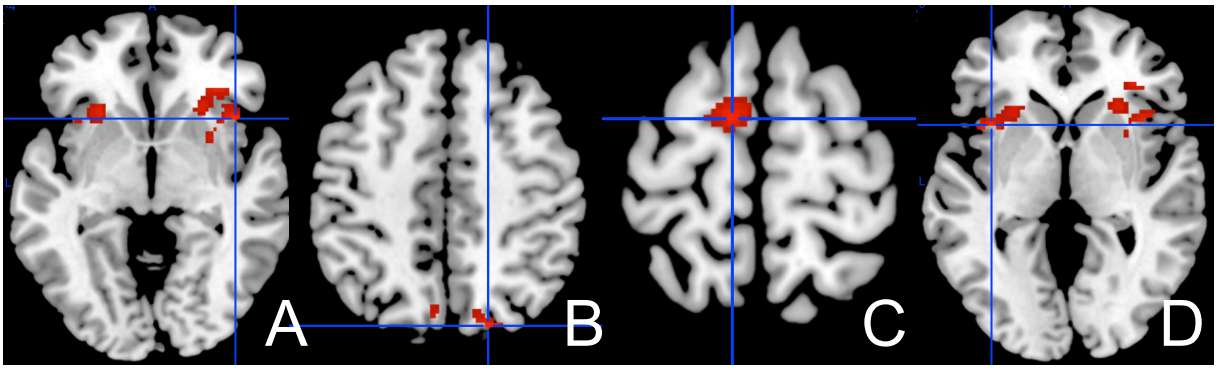


Figure 3: Group differences in brain activation between the ARMS-ST and the ARMS-LT groups.
The clusters reflect decreased regional brain activation in the right inferior frontal gyrus and insula (x=42; y=18; z=-4; voxels=303; P<0.05, panel A) and in bilateral precuneus (18 -78 48, voxels= 243, P<0.1, panel B) in ARMS-ST as compared to ARMS-LT group during the 2-back>0-back task. Covarying for GMV caused loss of significance in left superior frontal gyrus (-10 -4 66, voxels= 229, panel C), and in left insula (-38 14 0, voxels= 224, P<0.01, panel D). The left side of the brain is shown on the left side of the images.

Effects of antipsychotic medication on neurofunctional activation

The analyses were repeated after exclusion of all subjects on antipsychotic medication. With exception of one cluster in the right middle frontal gyrus that lost its significance, the same set of regions showed significant differences between the FEP and HC groups. The differences in brain activation between FEP and ARMS-LT groups remained unchanged with one new significant cluster appearing in the left subthalamic and lentiform nuclei (-10 -14 -6). The results of repeated analyses in ARMS-ST and ARMS-LT groups showed no differences in brain activations (Table 2).

Table 2: Group differences in brain activation.

Group comparisons	$p_{FWE-corr}$ clustel level	Voxels	MNI x y z	T at voxel level	Side	Brain region
FEP < HC	0.0001	3586	2 -56 46 -18 -56 62 -6 -62 52	4.92	R, L	PCu extending into SPL and cuneus (BA 7)
	0.0001	949	-12 2 62 -34 2 54 -20 14 52	4.62	L	SFG and MFG (BA 6)
	0.109 (0.024)	207	26 20 48 36 14 50 24 18 56	3.25	R	MFG and SFG (BA 6, 8)*+
FEP < ARMS-LT	0.0001	1568	-32 34 0 -26 22 -4 -26 28 4	4.54	L	IFG, insula and OFG (BA 47,13)+
	0.006	402	-14 0 60 -18 -2 72 -10 16 64	3.97	L	SFG (BA 6)
	0.0001	689	-34 26 18 -36 50 14 -48 16 46	3.55	L	IFG and MFG (BA 13, 10, 8)+
	0.006 (n.s.)	406	26 22 2 30 34 -2 34 24 14	3.82	R	IFG extending into insula (BA 47)*
ARMS-ST < HC	0.0001	2738	-8 -64 48 4 -56 46 -22 -78 40	4.82	L, R	SPL, Pcu (BA 7)
	0.022	312	-12 0 62 -14 10 52	3.81	L	SFG (BA 6, 32)
	0.0001	741	48 -44 52 52 -44 44 36 -64 60	3.20	R	IPL and SPL (BA 40, 7)
ARMS-ST < ARMS-LT	0.025 (0.056)	303	42 18 -4 34 34 -2 26 22 -2	3.69	R	Insula and IFG (BA 47, 13)*
	0.077 (0.023)	229	-10 -4 66 -18 -4 70	3.52	L	SFG (BA 6)*+
	0.083 (0.039)	224	-38 14 0 -26 20 -4 -28 20 6	3.51	L	Insula (BA 13, 47)*
	0.062	243	18 -78 48 28 -82 36 -2 -74 54	3.50	R, L	Pcu (BA 9, 17)

Brain activation differences calculated using ANCOVA analyses in BPM of 2-back>0-back contrast with two non-imaging covariates (gender, age) and one imaging covariate VBM-GM.
*Cluster changed its significance after covarying for GMV (P value without VBM–GMV imaging covariate in parentheses)
+Cluster lost its significance after exclusion of medicated individuals (8 FEP, 2 ARMS-LT)
There were no significant differences in contrasts: FEP>HC, ARMS-ST>HC, ARMS-LT<HC, ARMS-LT>HC, ARMS-ST>ARMS-LT, FEP<ARMS-ST, FEP>ARMS-ST, FEP>ARMS-LT.
Two clusters (with symbol+) lost its significance after exclusion of 10 medicated patients from our FEP<ARMS-LT analysis. There was one big subcortical cluster that became significant encompassing the left subthalamic and lentiform nucleus (MNI x,y,z: -10 -14 -6; 1143 voxels; P=0.0001, FWE corrected) and two smaller ones in the right middle and the superior frontal gyrus (42 -46 2; 324 voxels; P=0.017, FWE corrected) and in the left inferior parietal lobule (-32 -44 50; 299 voxels; P=0.024, FWE corrected).

Abbreviations: ARMS-ST – short-term ARMS; ARMS-LT – long-term ARMS ; BA - Brodman area, FEP - 'first-episode psychosis', FG - frontal gyrus, HC - healthy controls; IFG - inferior frontal gyrus; IPL - inferior parietal

lobule; MFG - middle frontal gyrus; Pcu - Precuneus; n.s. – non significant, OFG – orbital frontal gyrus; SFG - superior frontal gyrus; SPL - superior parietal lobule

DISCUSSION

With a multimodal image analysis we investigated individuals at high-risk of psychosis and patients with the established illness. We used BPM toolbox in order to differentiate between vulnerability-associated and psychosis-associated abnormalities in the neural substrate of working memory function in conjunction with volumetric data. Comparing ARMS-ST and HC revealed that vulnerability to psychosis was associated with a reduced activation in the bilateral superior and inferior parietal lobules as well as in the left superior frontal gyrus. Compared to ARMS-LT individuals, those with the ARMS-ST showed reduced activation in the right insula and inferior frontal gyrus. Comparing the FEP patients to the ARMS-LT subjects revealed that full-blown psychosis was associated with reduced activation in the bilateral inferior frontal gyrus extending into insula, and in left superior, inferior and middle frontal gyri.

We recorded the time from the first presentation of subjects with ARMS and divided them into two subgroups comparable with the new staging model for psychosis (McGorry et al., 2009). The mean duration of the ARMS was 4.5 years in the ARMS-LT group; thus the probability that any of these subjects would develop psychosis in the future was rather low (Cannon et al., 2008; Riecher-Rössler et al., 2009). In the ARMS-ST subjects, we expect a transition rate of approximately 30% (Mechelli, 2010; Riecher-Rössler et al., 2009) in the next one–two years. Splitting the ARMS subjects into two groups allows a better understanding of a real subsequent probability to develop psychosis. This may help to investigate psychosis-associated functional abnormalities in the FEP (individuals with psychosis itself) in contrast to the ARMS-LT (individuals with vulnerability but very low transition probability to psychosis). This particular comparison removes any psychosis specific effects (inherent in the 30% of ARMS who might transit) making the ARMS-LT versus FEP comparison a 'purer' contrast to psychosis. The ARMS-ST group with 30% probability to develop psychosis subsequently was a basis to investigate vulnerability connected with higher transition probability-associated changes in brain activation compared to the HC. Interestingly, our ARMS-LT did not differ from the ARMS-ST with respect to age, even included longer time ago in ARMS. This could be because of small sample sizes and needs further investigation. On the other hand, the difference between ARMS-ST and ARMS-LT are not attributable to the effect of aging in one of those groups. We can speculate that the differences between these two groups in the n-back activation network showed not only disrupted function in the ARMS-ST group, but resilience or protective processes in the ARMS-LT group.

The present study was powered to detect group effects on activation rather than on task performance. However, the two ARMS groups showed differences in reaction times during the most demanding condition. The FEP and ARMS-ST groups needed longer during 2-back condition compared to the HC and the ARMS-LT groups. According to the previously published studies (Delawalla et al., 2008; Sanz et al., 2009) the FEP and ARMS-ST groups might be lower performing and show prefrontal hypo-activation. There is evidence indicating that working memory functioning in prodromal psychosis is related to striatal dopaminergic alterations in a non-linear (i.e. U curve) fashion (Fusar-Poli et al., 2010b). However, it may be because all group contrasts were based on 2-back > 0-back condition, it means when

the task gets harder. Thus, the compensation model might predict hypo-activation (Callicott et al., 2003b) due to a ceiling effect of going downwards on the inverted U-shaped curve. Individuals with more psychotic symptoms (FEP, ARMS-ST) thus could reach the peak of the inverted U-curve sooner than less symptomatic (ARMS-LT and HC) individuals. Apart from that the behavioral differences may be due to attentional impairments seen in schizophrenia patients (Karch et al., 2009), the symptom severity, and medication. Previous studies report impaired working memory performance in the ARMS (Eastvold et al., 2007; Pflueger et al., 2007), although other studies find no effect on task performance in the ARMS (Broome et al., 2010; Broome et al., 2009; Fusar-Poli et al., 2010a; Fusar-Poli et al., 2010b) or in the FEP (Ettinger et al., 2011). However, functional neuroimaging techniques are able to detect physiological changes, and are likely to be more sensitive than behavioural measures (Wilkinson and Halligan, 2004). Furthermore, the image analyses were restricted to correct responses and the observed differential activations reflect differences at the neurophysiological level and not on task performance.

Overall, we found working memory-associated activations in the prefrontal and parietal cortex in all our subjects during WM task, corresponding to previously published data of patients with an ARMS (Broome et al., 2009; Fusar-Poli et al., 2010a) and psychosis (Callicott et al., 2003a; Callicott et al., 2003b; Forbes et al., 2009). Vulnerability-associated functional abnormalities in the superior frontal gyrus and in parietal lobules distinguished the ARMS-ST from HC group and corresponded to the previous fMRI studies with altered prefrontal brain activation (Fusar-Poli et al., 2009; Fusar-Poli et al., 2010b) for review see reference (Fusar-Poli et al., 2007a). Compared to the HC, both the ARMS-ST and ARMS-LT groups showed reduced GMV in the anterior cingulate, middle and inferior frontal gyri. These findings are similar to the published volumetric abnormalities found in ARMS (Borgwardt et al., 2008; Borgwardt et al., 2007b; Fornito et al., 2008; Koutsouleris et al., 2009; Meisenzahl et al., 2008; Pantelis et al., 2003; Sun et al., 2009) and to those found at meta-analytical voxel-based level (Fusar-Poli et al., 2011). Interestingly, we found probably compensatory more GMV in insula in the ARMS-LT compared to the HC group.

The neurofunctional reduction in the ARMS-ST versus ARMS-LT group revealed the difference between the higher and lower transition probability. Only one cluster in the right inferior frontal gyrus and insula distinguished these two groups after covarying for gray matter volume using BPM. Furthermore, reduced activation in the left inferior frontal gyrus, the right insula, and in the bilateral precuneus positively correlated with volumetric deficits in these regions within the ARMS-LT and ARMS-ST individuals, respectively. A previous study by Fusar-Poli et al. (Fusar-Poli et al., 2010a) showed that the prefrontal functional abnormalities in ARMS are related to GMV. Our results are comparable to the prefrontal abnormalities found in ARMS (Fusar-Poli et al., 2010a) and to the altered function found in precuneus in unaffected siblings of schizophrenia patients (Liu et al., 2010). Furthermore, reduced GMV in the right temporal gyrus and insula delineate the difference between the ARMS-ST and the ARMS-LT group. These are the regions known to be different in ARMS with and without subsequent transition to psychosis (Borgwardt et al., 2007b).

Comparing the FEP with ARMS-LT individuals, we observed functional differences in the bilateral inferior frontal gyrus and insula, and in left superior and middle frontal gyrus, that may delineate psychosis-associated changes. These functional alterations during the WM task resemble those reported previously in schizophrenia patients in prefrontal (Barch et al., 2001; Cannon et al., 2005; Johnson et al., 2006; Manoach et al., 2000; Manoach et al., 1999; Menon et al., 2001; Perlstein et al., 2001; Tan et al., 2005), and temporal (Fusar-Poli et al., 2007a; Glahn et al., 2005; Karch et al., 2009; Schneider et al., 2007) regions.

In agreement with our hypothesis, the ARMS-LT and the ARMS-ST groups showed more WM-related activation than the FEP and less than the HC group. We found neither neurofunctional nor behavioral differences between FEP and ARMS-ST group. Taking into account 20-30 % transition probability to the psychosis, the major part of this group will subsequently belong to the ARMS-LT group, physiologically different from the FEP group. We can deduce that the ARSM-LT group has not only lower transition probability (Riecher-Rössler et al., 2009) but as well some resilience factors, which helped those individuals to avoid the imminent psychosis.

The ARMS is understood as a dynamic process (Simon and Umbricht, 2010; Yung et al., 2010) concerning structural and functional brain abnormalities (Fusar-Poli et al., 2007a), disrupted cellular integrity and connectivity (Green, 2007), and other still unknown factors. We showed that neurofunctional abnormalities are associated with structural deficits in the ARMS-ST and ARMS-LT groups, as they changed its significance in insular and inferior and superior frontal regions after covarying for GMV. Using a well-established working memory paradigm, we found functional vulnerability-associated abnormalities in a fronto-parietal network, whereas abnormalities associated with psychosis itself in frontal and insular brain activations. We presume that dynamic processes in task-relevant regions underline positive functional-structural correlation in the early stages of ARMS (ARMS-ST, ARMS-LT) and the negative correlation in the FEP group. It remains unknown, whether functional abnormalities precede the structural ones, how reversible they are, and if they are compensatory in their nature. In future, a multimodal approach combining fMRI and sMRI results with connectivity measurements or combining optical and genetic techniques(Lee et al., 2010b) could help to improve understanding of neural circuits underlying psychosis and ARMS.

The neurofunctional abnormalities we observed could not directly be attributed to antipsychotic treatment, as all of the ARMS-ST were antipsychotic-naïve and only 12% of the ARMS-LT had antipsychotic treatment at the time of scanning. Although the exclusion of 38% antipsychotic-medicated FEP patients did not substantially change our results, we probably found a protective effect of antipsychotics in the subcortical structures. For all other comparisons after excluding medicated individuals from analyses the results remained largely unchanged. The influence of antipsychotics on the brain function is not entirely clear, however antipsychotics may affect neural activity (Lui et al., 2010) and GMV (Tost et al., 2010), especially in basal ganglia (Smieskova et al., 2009). Furthermore, all of those on antipsychotics were treated with atypical compounds in very low doses.

Some limitations of this study should be considered. Firstly, although one subject of the ARMS-ST group developed psychosis during the follow-up, the small sample size did not allow meaningful analyses regarding the clinical outcome. Secondly, our specific FEP population included mostly outpatients at the beginning of their disease with relatively high premorbid IQ values compared to chronically ill psychotic patients at a later stage of the illness (Urfer-Parnas et al., 2010). Thirdly, although the FEP group had less formal education than the other groups, this could not account for the differences between the ARMS-ST and ARMS-LT and control groups, which were matched regarding these aspects. Fourthly, although the ARMS-ST group has a higher probability of transition to psychosis, thus there is a non-transition probability of approximately 70%. The neurofunctional differences found in this group could be even more pronounced in the pure transition subgroup. Fifthly, we have not examined the association with an affective psychosis, borderline personality disorder or other comorbidities with the ARMS. Assessment of other psychopathological measures could lead to better distinction characteristics of ARMS-ST and ARMS-LT group. However, this was not the main aim of the study. Sixthly, we have not studied the default mode network independent of the WM-task and cannot thus exclude the anomalous network connectivity (Whitfield-Gabrieli et al., 2009) in included individuals. Such functional connectivity analysis could extend the understanding of ARMS-underlying processes. Finally, the pure transition group could show more pronounced differences, but the differences seen even at the very early beginning of the ARMS in ARMS-ST, showed us the regions playing the crucial role in the dynamic ARMS process.

CONCLUSION

In this study we found distinct patterns of mnemonic neurofunctional brain activation related to vulnerability to psychosis as opposed to psychosis itself. Neurofunctional alterations in fronto-parietal regions may be correlates of vulnerability to psychosis whereas more pronounced neurofunctional abnormalities in prefrontal cortex were associated with the presence of psychosis. Our results thus confirm the hypothesis of a disrupted working memory network during the development of psychosis. Additionally, neurofunctional differences within the ARMS were related to different duration of ARMS. These abnormalities were directly related to volumetric reduction.

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All authors declare that they have no conflicts of interest.

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Chapter 5

SUMMARY AND DISCUSSION

A task to improve the understanding of the psychosis, its cause, course and prevention is extremely complex. Studying populations suffering from schizophrenia means to take into account many confounding factors that make the investigation even more complex. Based on the known effect of antipsychotics on brain volume (Dazzan, et al. 2005; Konopaske, et al. 2008), we wanted to uncover the differences between psychotic individuals medicated with different types of antipsychotics.

Secondly, we aimed at characterizing the vulnerability markers of psychosis in individuals who are at high risk to develop psychosis and have minimum of confounders influencing the results. We did so in our meta-analysis of existing studies, comparing individuals prone to transition to psychosis according to their subsequent outcome – with or without later transition to psychosis.

Thirdly, we wanted to improve understanding of vulnerability- and psychosis-associated abnormalities in population of antipsychotic-naive subjects. We introduced a new concept of splitting ARMS population according to the duration of the risk-state and their probability to transit to psychosis. The criterion to split ARMS according to the duration of their risk-state was assigned at two years after ascertainment and was based on differences in transition probability. In our two groups with different transition probabilities we compared their gray matter volumes and investigated working memory-related neurofunctional differences in brain activation.

In **chapter 4.1**, twenty-four longitudinal and six cross-sectional studies of schizophrenic patients with antipsychotic medication were reviewed. We investigated the effect of antipsychotics on the brain structure in schizophrenia and found reduced gray matter volume particularly in the frontal and temporal lobes. Structural neuroimaging studies indicate that treatment with typical as well as atypical antipsychotics may affect regional gray matter volume. Studies with typical antipsychotics reported increased gray matter in the cingulate cortex, in contrast to the atypical antipsychotics with the excess more often seen in the thalamus. Our conclusions of antipsychotic-related alterations of brain structure in schizophrenia have been recently confirmed by a long-term follow-up study in 211 patients (Ho, et al. 2011b).

Neuroimaging predictors of later transition to psychosis were analyzed in **chapter 4.2.** The meta-analysis showed that total brain volume and total gray matter volume were increased in individuals who made transition to psychosis compared to the individuals without transition, but as well as to the first episode of psychosis individuals. At the other side we found reduced regional gray matter volume in insula, anterior cingulate, prefrontal cortex, and cerebellum. Thus, vulnerability markers to psychosis seem to be subtle and region-specific. The counter-intuitive increased global brain volume in the group of ARMS who made transition could reflect efforts of the brain to compensate for regional abnormalities. This compensatory increment could involve various cellular processes not only in neurons, but as well as in the neuropil. A recent longitudinal study of first-episode patients with minimal antipsychotic treatment

before study enrolment showed that less illness severity was associated with increased brain tissue volumes (Ho, et al. 2011b). This result correspond to our finding of increased total brain volume and total gray matter volume in the ARMS-T individuals with less sever symptoms as compared to the first episode patients.

Meta-analysis of functional studies showed reduced activation in regions where we found regional volumetric deficits: prefrontal and cingulate cortex and in occipital lobe. Those structural and functional results are not confounded by medication and could be seen as neuroimaging predictors of transition to psychosis.

Chapter 4.3 showed structural differences in ARMS individuals with different transition probabilities to psychosis and putative resilience factors. Compared to the ARMS-LT, the ARMS-ST group expressed significant reductions in grey matter volume in prefrontal, insular and middle temporal areas, consistently implicated in volumetric neuroimaging studies of high-risk individuals for schizophrenia (Borgwardt, et al. 2007a; Borgwardt, et al. 2008; Borgwardt, et al. 2007b; Koutsouleris, et al. 2009; Pantelis, et al. 2003a; Takahashi, et al. 2009a; Takahashi, et al. 2009b). Comparing the ARMS-ST to the ARMS-LT subjects showed increase of the right insular volume. Interestingly, this gray matter volume (GMV) increase was detectable also in the ARMS-LT compared to the HC group. Therefore, the increase of the right insular volume could be associated with the resilience factors. Contrary to that, the reduced right insular volume was associated with higher transition probability. Negative symptoms correlated negatively and global functioning positively with volumetric differences between ARMS.

Working memory related brain activation was a basis to investigate neurofunctional differences between individuals at high-risk of psychosis and patients with the established illness. In **chapter 4.4** we showed that neurofunctional abnormalities were associated with structural deficits in the ARMS-ST and ARMS-LT groups. The neurofunctional abnormalities changed their significance in insular and frontal regions after covarying for GMV. Using a working memory paradigm, we found functional vulnerability-associated abnormalities in a fronto-parietal network, whereas abnormalities associated with psychosis itself in frontal and insular brain activations.

Vulnerability-associated altered prefrontal brain activation corresponded to the previous fMRI review (Fusar-Poli, et al. 2007a). Reduced activation in the inferior frontal, insular, and precuneus regions positively correlated with volumetric deficits in these regions within the ARMS-LT and ARMS-ST individuals, corresponding to the previous studies (Fusar-Poli, et al. 2010c; Liu, et al. 2010). Psychosis-associated functional alterations in frontal gyri and insula during the WM task resemble those reported previously in schizophrenia patients in prefrontal (Barch, et al. 2001; Cannon, et al. 2005; Johnson, et al. 2006; Manoach, et al. 2000; Manoach, et al. 1999; Menon, et al. 2001; Perlstein, et al. 2001; Tan, et al. 2005), and temporal regions (Fusar-Poli, et al. 2007a; Glahn, et al. 2005; Karch, et al. 2009; Schneider, et al. 2007).

Limitations

Several limitations of our studies must be acknowledged. First of all, using neuroimaging methods does not enable us to detect direct pathophysiological differences such as neuronal or glial loss or abnormalities at the receptor level. The differences we have detected are delimitated by white or gray matter volume and by difference in oxygenated and deoxygenated blood in the VBM and in the fMRI study, respectively. It is extremely important to formulate the MRI results and implications very carefully and truthfully.

Secondly, fMRI, that allows *in vivo* investigation of the human brain in terms of various blood flows in different brain regions, is not able to identify the neural networks underlying specific condition. The existence of different imaging packages (e.g. SPM – parametric and XBAMM – non-parametric analysis) contributes to the heterogeneity of findings (Fusar-Poli, et al. 2010a).

Thirdly, although VBM allows comparison of the whole brain at the single voxel level, there are still relevant problems connected to the brain registration (Ashburner and Friston 2000), smoothing kernel and labeling of results according to the human brain atlases and probabilistic brain maps. Furthermore, exact meaning of the volumetric abnormalities could reflect various neuropathological changes, e.g. impaired structure of neurons and glial cells, or neurotoxic effect of various substances. Furthermore, different scanning parameters and analytical approaches contribute to the inconsistencies in MRI measures.

Fourthly, our analyses are based on the between-group comparison and thus do not allow any prediction for individual patients. It is necessary to reproduce our and others' results and to provide bigger multicenter studies aiming on characterizing vulnerability markers for transition to psychosis that could be used in a clinical praxis. The criterion to split ARMS according to the duration of their risk-state, assigned on the two years after ascertainment, helps to distinguish between vulnerability- and resilience-associated factors. However, the relevance of this new approach needs to be confirmed in a longitudinal follow-up study that we are currently planning.

Fifthly, assessment of other psychopathological measures (affective psychosis, borderline personality disorder or other comorbidities) could lead to better distinction characteristics of ARMS-ST and ARMS-LT group. The subsequent analyses with bigger sample sizes and with orientation on diagnoses could help to investigate these aspects.

Sixthly, although our studies included follow up of clinical outcome, MR scanning was done at baseline. However, when comparing different groups of subjects, it is difficult to control for effects related to other variable than the parameter of interest. This potential confound can be overcome in a longitudinal design. Re-scanning individuals after their transition to psychosis or after subsequent setting of other psychiatric diagnosis could improve the understanding of vulnerability and resilience factors.

Conclusions and implications

Brain structural abnormalities in individuals treated with antipsychotics were clearly associated with an effect of antipsychotic medication. Both types of antipsychotic medication led to the changes in the brain structure in regional and global measures. This evidence indicates the importance of reasonable and well-monitored use of antipsychotics, in particular in off-label conditions as high-risk individuals (Simon and Umbricht 2010; Ziermans, et al. 2010).

We showed in our meta-analysis that individuals with later transition to psychosis (ARMS-T) compared to those without transition (ARMS-NT) had neuroanatomical and neurofunctional abnormalities in prefrontal, cingulate, temporal, and cerebellar cortex. They correspond to the neurocognitive abnormalities in high-risk individuals (Fusar-Poli, et al. 2007a).

Majority of studies concentrate on the individuals with later transition to psychosis, ARMS-T. The larger proportion of ARMS individuals remains virtually neglected. Based on these facts, we argue that the ARMS-LT could help us to better understand compensatory or resilient processes in high-risk individuals. Their potential psychiatric diagnoses could help us to understand comorbidities and similar characteristics with other symptoms.

Structural deficits in ARMS were associated with the decline in functioning and with negative symptoms. Vulnerability-associated structural abnormalities were found in orbitofrontal network, whereas abnormalities associated with higher transition probability to psychosis in insular and middle temporal brain regions. Resilient volumetric changes could be detected in in the ARMS-LT group with lower probability for transition to psychosis.

Mnemonic neurofunctional alterations in fronto-parietal regions may be correlates of vulnerability to psychosis whereas more pronounced abnormalities in prefrontal cortex are associated with the presence of psychosis. Additionally, neurofunctional differences within the ARMS were related to different duration of ARMS. These abnormalities were directly related to volumetric reduction. We used multimodal approach to investigate functional and structural imaging data in conjunction and tried to characterize neuroanatomical and neurofunctional correlates of liability to psychosis. In future, multivariate neuroimaging analyses (e.g. support vector machine (Koutsouleris, et al. 2010)) could help to predict the disease transition on an individual level.

Chapter 6

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List of publications

- **Smieskova R.,** Fusar-Poli P., Aston J., Simon A., Bendfeldt K., Lenz C., Stieglitz R. D., McGuire P., Riecher-Rössler A., Borgwardt S.J. Different transition probabilities to psychosis associated with insular volume abnormalities – A VBM study, submitted
- **Smieskova R.,** Allen P., Simon A., Aston J., Bendfeldt K., Drewe J., Gruber K., Gschwandtner U., Klarhoefer M., 3enz C., Scheffler K., Stieglitz R.D.,McGuire P.K., Riecher-Rössler A., Borgwardt S.J., 2011. Different duration of at-risk mental state associated with neurofunctional abnormalities – A multimodal imaging study, Hum Brain Mapp, in press
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Posters at national and international conferences

- Different duration of at-risk mental state associated with neurofunctional abnormalities – A multimodal imaging study. Poster presentation on the Annual Meeting of the Swiss Society for Neuroscience, Basel, March 2011.
- Vulnerability- versus psychosis-associated brain functional abnormalities during memory processing – A multimodal imaging study. Poster presentation on the 7th International Conference on Early Psychosis, Amsterdam, Netherlands, November 2010.
- A meta-analysis of neuroimaging predictors of transition to psychosis. Poster presentation on the ECNP Workshop on Neuropsychopharmacology for Young Scientists in Europe Nice, France, March 2010.
- The effects of antipsychotics on brain structure – a systematic review. Poster presentation on the annual conference of Swiss Society of biological Psychiatry (SSBP) and Swiss Society of Sleep Research, Sleep Medicine and Chronobiology (SSSC) in Bern, Switzerland, March 2009.

Chapter 7

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