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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	No	12	32	↓ short insula R	↓ GM in L, R insula	Not studied
			1	16 f-up	12–48	35	↓: insula by 0.4%/year	↓ GM in insula by 0.6%/year	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.

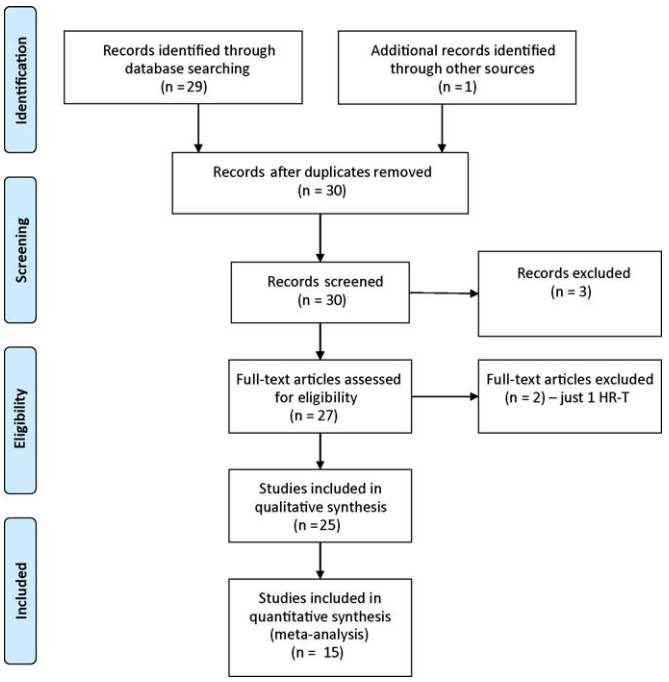

Fig. 1. Flowchart of the studies considered and included according to the design.

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).

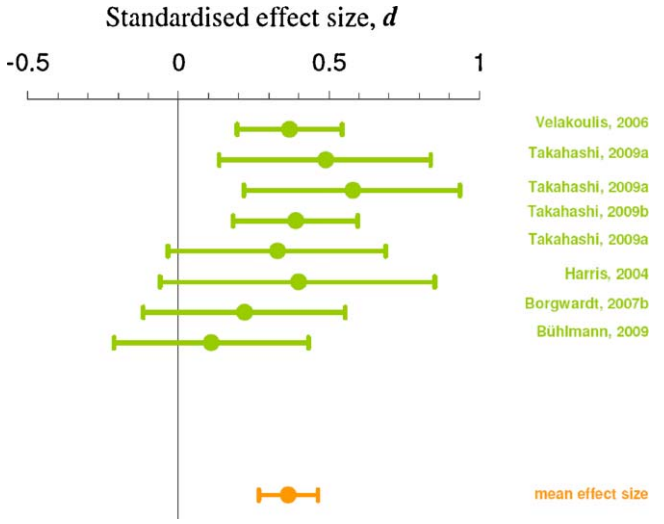

Fig. 2. Mean effect size (Cohen's d) and confidence interval (95% CI) of whole brain volume (WBV) (Velakoulis et al., 2006; Harris et al., 2004), total intracranial volume (ICV) (Takahashi et al., 2009a,b) and total gray matter volume (GMV) (Takahashi et al., 2009a,b; Borgwardt et al., 2007b; Buehlmann 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. 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.

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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