◆ Human Brain Mapping 33:2281–2294 (2012) ◆

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 (WM) 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 WM task. We examined functional magnetic resonance imaging (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 with 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 with 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 with the ARMS-LT, the ARMS-ST subjects showed reduced activation

Additional Supporting Information may be found in the online version of this article.

Contract grant sponsor: Swiss National Science Foundation (to R.S. and S.J.B.); Contract grant number: 3232BO_119382; Contract grant sponsor: Novartis Foundation; Contract grant sponsor: Honoraria for lectures and consultancy fees from Lilly (to S.J.B.).

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Received for publication 4 February 2011; Revised 22 March 2011; Accepted 26 April 2011

DOI: 10.1002/hbm.21360

Published online 16 September 2011 in Wiley Online Library (wileyonlinelibrary.com).

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 WM task. Neurofunctional differences within the ARMS were related to different duration of the prodromal state and resilience factors. *Hum Brain Mapp 33:2281–2294, 2012.*

Key words: ultra-high-risk (UHS); at-risk mental state (ARMS); schizophrenia; working memory; fMRI; psychosis

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-Rossler et al., 2007, 2009; Yung et al., 2004) or functional decline. These psychopathological symptoms are often associated with negative (Lencz et al., 2004; Riecher-Rossler et al., 2009) symptoms, subtle cognitive deficits (Brewer et al., 2006; Riecher-Rossler et al., 2009), and include deficits in WM function (Broome et al., 2010; Simon et al., 2007). Those with the ARMS have a 20–40% probability of developing the psychosis (Riecher-Rossler et al., 2007, 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-Rossler et al., 2009).

Over the past decade, structural magnetic resonance imaging (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., 2006, 2007a,b, 2008; 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 WM tasks (Broome et al., 2009, 2010; 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-Rossler et al., 2009). Importantly, 19 of those 21 ARMS individuals who made transition, transit in the first 2 years after their ascertainment. Afterwards, only 2 of 53 included ARMS individuals made transition to psychosis (Riecher-Rossler et al., 2009) representing a reduced transition probability. Similarly, the vast majority of transitions occur in the first 2 years (estimated hazard ratio 0.58) and significantly dropped over time (estimated hazard ratio 0.07) (Yung et al., 2007). In this study, we therefore 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) 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 versus 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., 2009, 2010; Fusar-Poli et al., 2010, 2011c) investigating neurofunctional abnormalities while performing a WM task. Expanding the previous study (Broome et al., 2009), here we investigated an ARMS-LT group with a lower probability of developing psychosis compared with the ARMS-ST group (Yung et al., 2007).

In addition, 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 with the healthy control (HC) group.
2. The ARMS-ST group would show more functional deficits associated with volumetric abnormalities compared with the ARMS-LT group.

Abbreviations

ANCOVA	analysis of covariance
ARMS	at-risk mental state
ARMS-LT	long-term ARMS
ARMS-ST	short-term ARMS
BLIPS	brief limited intermittent psychotic symptoms
BPM	biological parametric mapping
BPRS	brief psychiatric rating scale
BSIP	basel screening instrument for psychosis
EPPIC	early psychosis prevention and intervention centre
FEP	first-episode psychosis
FWE	family-wise error
fMRI	functional magnetic resonance imaging
GAF	global assessment of functioning
GMV	gray matter volume
HC	healthy control
LSD	least-significant difference
PACE	personal assessment and crisis evaluation
SANS	scale for the assessment of negative symptoms
sMRI	structural magnetic resonance imaging
VBM	voxel-based morphometry
WM	working memory

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-Rossler 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,b; Pantelis et al., 2003; Sun et al., 2009; Takahashi et al., 2009a,b; Velakoulis et al., 2006; Walterfang et al., 2008; Wood et al., 2003, 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-Rossler et al., 2008; Yung et al., 1998) but had different probabilities of developing psychosis (Cannon et al., 2008; Riecher-Rossler 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 3 × 40 mg/day, and 1 aripiprazole 5 mg/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 antidepressants precluded an analysis of putative neurofunctional effects of antidepressants (Fusar-Poli et al., 2007b).

The FEP patients ($n = 21$) were defined as subjects who met the operational criteria for 'FEP'(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 (seven of them antipsychotic-naïve, six antipsychotic-free) at time of scanning. Eight FEP patients were receiving antipsychotics at the time of scanning for approximately 2 months (five quetiapine and two 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-Rossler et al., 2007, 2008), 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-Rossler 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-Rossler 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 76×76, 126 volumes and 38 slices with 0.5 mm interslice gap, providing a resolution of $3 \times 3 \times 3$ mm^3, and a field of view (FOV) 228×228 cm^2. With an inter-stimulus interval of 2 s, all subjects saw the series of black letters on the white background in a prismatic mirror. Each stimulus was presented for 1 s. The size of the letters was 8 cm projected on the screen at the end of the scanner. All participants with myopie 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 ($2 \times$ 1-back, $3 \times$ 2-back, and $5 \times$ 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 $1 \times 1 \times 1$ mm^3 isotropic spatial resolution and with inversion time of 1,000 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 haemodynamic 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 WM 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 four 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 oxygenation 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 to infer statistical significance. To provide sufficient details about this 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 et al., 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 I). For post-hoc analyses we used the least-significant difference (LSD) test. 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 (BPRS) and negative (SANS) symptoms, and in global functioning (GAF) 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 with the ARMS-LT (Table I).

N-Back Task Performance

There was no difference in the accuracy in any of conditions. Reaction times were significantly longer in the FEP compared with the HC and ARMS-LT groups and in the ARMS-ST compared with the HC and ARMS-LT groups (Supporting Information Table I).

Gray Matter Volumes (VBM Results)

The FEP group showed reduced GMV in the anterior cingulo-prefrontal, hippocampal, and occipito-cerebellar regions, compared with HC group ($P < 0.01$). Compared with the ARMS-LT, the FEP group had temporo-insular volumetric reductions ($P < 0.005$). Compared with 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 with the HC group ($P < 0.05$). There was more GMV in insula in the ARMS-LT group compared with the HC group. The ARMS-ST showed volumetric reductions in the temporal gyrus extending into insula, compared with the ARMS-LT group (Supporting Information Table II).

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

TABLE I. Demographic and clinical characteristics

Characteristic	FEP ($n = 21$)	ARMS-ST ($n = 17$)	ARMS-LP ($n = 16$)	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; ST—some times.

TABLE II. Group differences in brain activation

Group comparisons	$p_{FWE\text{-}corr}$ clustel level	Voxels	MNI x	MNI y	MNI z	*T* at voxel level	Side	Brain region
FEP < HC	0.0001	3,586	2	−56	46	4.92	R, L	PCu extending into SPL and cuneus (BA 7)
			−18	−56	62			
			−6	−62	52			
	0.0001	949	−12	2	62	4.62	L	SFG and MFG (BA 6)
			−34	2	54			
			−20	14	52			
	0.109	207	26	20	48	3.25	R	MFG and SFG (BA 6, 8)[a,b]
	(0.024)		36	14	50			
			24	18	56			
FEP < ARMS-LT	0.0001	1,568	−32	34	0	4.54	L	IFG, insula, and OFG (BA 47,13)[b]
			−26	22	−4			
			−26	28	4			
	0.006	402	−14	0	60	3.97	L	SFG (BA 6)
			−18	−2	72			
			−10	16	64			
	0.0001	689	−34	26	18	3.55	L	IFG and MFG (BA 13, 10, 8)[b]
			−36	50	14			
			−48	16	46			
	0.006	406	26	22	2	3.82	R	IFG extending into insula (BA 47)[a]
	(n.s.)		30	34	−2			
			34	24	14			
ARMS-ST < HC	0.0001	2,738	−8	−64	48	4.82	L, R	SPL, Pcu (BA 7)
			4	−56	46			
			−22	−78	40			
	0.022	312	−12	0	62	3.81	L	SFG (BA 6, 32)
			−14	10	52			
	0.0001	741	48	−44	52	3.20	R	IPL and SPL (BA 40, 7)
			52	−44	44			
			36	−64	60			
ARMS-ST < ARMS-LT	0.025	303	42	18	−4	3.69	R	Insula and IFG (BA 47, 13)[a]
	(0.056)		34	34	−2			
			26	22	−2			
	0.077	229	−10	−4	66	3.52	L	SFG (BA 6)[a,b]
	(0.023)		−18	−4	70			
	0.083	224	−38	14	0	3.51	L	Insula (BA 13, 47)[a]
	(0.039)		−26	20	−4			
			−28	20	6			
	0.062	243	18	−78	48	3.50	R, L	Pcu (BA 9, 17)
			28	−82	36			
			−2	−74	54			

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. 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 (indicated with "b") 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., nonsignificant; OFG, orbital frontal gyrus; SFG, superior frontal gyrus; SPL, superior parietal lobule.

[a]Cluster changed its significance after covarying for GMV (*P* value without VBM–GMV imaging covariate in parentheses).

[b]Cluster lost its significance after exclusion of medicated individuals (8 FEP, 2 ARMS-LT).

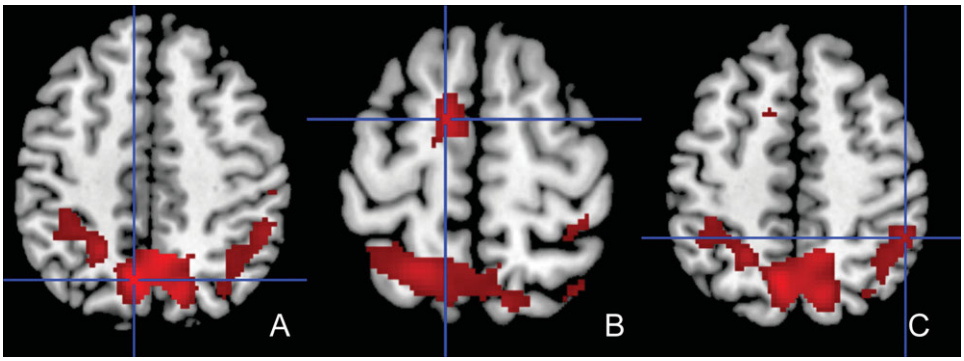

Figure 1.

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 with 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. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

of group. We used this task effect as a mask to constrain subsequent group analyses to a WM network (Supporting Information Figure).

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 II, Fig. 1). The ARMS-LT group showed no significant functional differences compared with the HC group.

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 with the HC group. Compared with 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 II, Fig. 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 with the ARMS-ST group.

Neurofunctional abnormalities associated with high probability to develop psychosis

Compared with 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 ($P < 0.1$) (Fig. 3; Table II). 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.

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 II).

DISCUSSION

With a multimodal image analysis, we investigated individuals at high-risk of psychosis and patients with the established illness. We used the BPM toolbox to differentiate between vulnerability-associated and psychosis-associated abnormalities in the neural substrate of WM 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

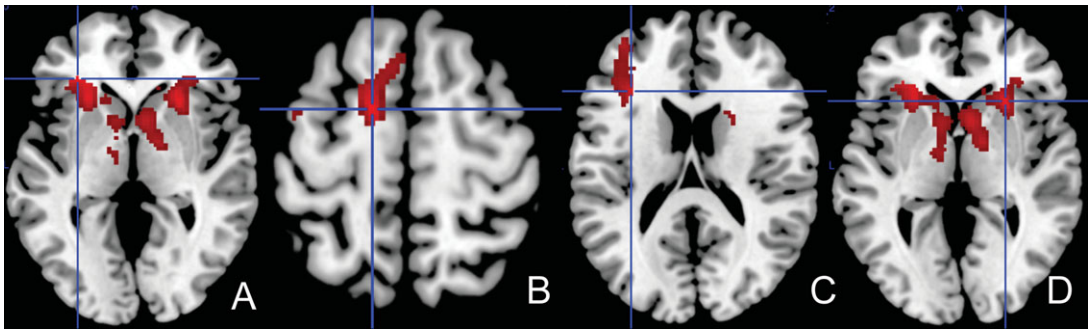

Figure 2.

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 with 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. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

frontal gyrus. Compared with ARMS-LT individuals, those with the ARMS-ST showed reduced activation in the right insula and inferior frontal gyrus. Comparing the FEP patients with 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-Rossler et al., 2009). In the ARMS-ST subjects, we expect a transition rate of approximately 30% (Mechelli,2010; Riecher-Rossler et al., 2009) in the next 1–2 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

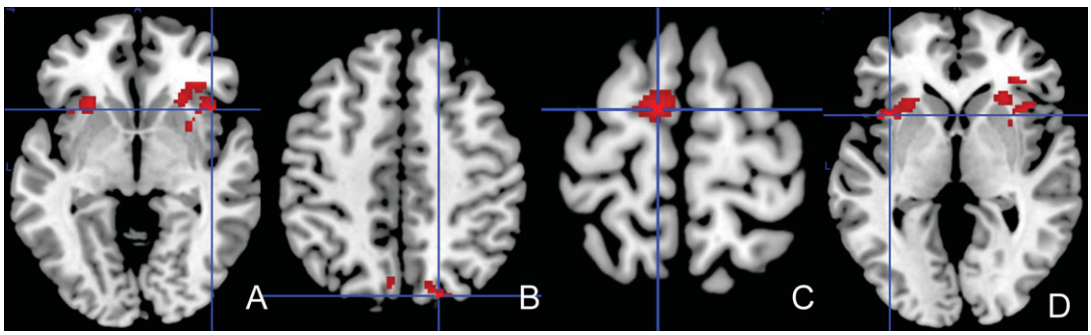

Figure 3.

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 with 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. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

basis to investigate vulnerability connected with higher transition probability-associated changes in brain activation compared with 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.

This 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 with 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 WM functioning in prodromal psychosis is related to striatal dopaminergic alterations in a non-linear (i.e., U curve) fashion (Fusar-Poli et al., 2010). 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 WM performance in the ARMS (Eastvold et al., 2007; Pflueger et al., 2007), although other studies found no effect on task performance in the ARMS (Broome et al., 2009, 2010; Fusar-Poli et al., 2010, 2011c) 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 behavioral 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 WM-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., 2011c) and psychosis (Callicott et al., 2003a,b; 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., 2010, 2011b), for review see reference Fusar-Poli et al., 2007a. Compared with 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., 2007b, 2008; 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., 2011a). Interestingly, we found probably compensatory more GMV in insula in the ARMS-LT compared with 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 GMV 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. (2011c) showed that the prefrontal functional abnormalities in ARMS are related to GMV. Our results are comparable with the prefrontal abnormalities found in ARMS (Fusar-Poli et al., 2011c) 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., 1999, 2000; 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-Rossler et al., 2009) but also 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 WM 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. First, 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. Second, our specific FEP population included mostly outpatients at the beginning of their disease with relatively high premorbid IQ values compared with chronically ill psychotic patients at a later stage of the illness (Urfer-Parnas et al., 2010). Third, 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. Fourth, 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. Fifth, 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. Sixth, 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, suggested a crucial role of neurofunctional abnormalities in the dynamic process of transition to psychosis.

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 WM network during the development of psychosis. In addition, neurofunctional differences within the ARMS were related to different duration of ARMS. These abnormalities were directly related to volumetric reduction.

ACKNOWLEDGMENTS

The authors acknowledge the contribution of the subjects who took part in this study and they thank the FEPSY study group for recruitment and management of participants.

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