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Neuroanatomical correlates of executive dysfunction in the at-risk mental state for psychosis

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ABSTRACT

Deficits in executive functioning have been described as a core feature of schizophrenia and have been linked to patterns of fronto-temporo-limbic brain alterations. To date, such structure–cognition relationships have not been explored in a clinically defined at-risk mental state (ARMS) for psychosis using whole-brain neuroimaging techniques. Therefore, we used voxel-based morphometry in 40 ARMS and 30 matched healthy control (HC) individuals to investigate whether gray and white matter volumes (1) correlated with the performance in the Trail-Making Test B (TMT-B), an established measure of executive functioning, and (2) were volumetrically linked to the ventromedial prefrontal cortex (VMPFC), found to be associated with TMT-B in the ARMS during the first analysis step. We found the ARMS subjects to be specifically impaired in their TMT-B performance versus HC. Brain-cognition associations involving the insular cortices were observed in the HC, but not in the ARMS individuals. Conversely, TMT-B correlations in the VMPFC, the cerebellum, the fronto-callosal white matter were detected in the ARMS, but not the HC group. The VMPFC was linked to the temporo-limbic cortices in HC, whereas the connectivity pattern in the ARMS involved the left temporal and dorsolateral prefrontal cortex, the cerebellum, the right SMA and extended portions of the fronto-callosal white matter. These findings suggest that executive deficits are already present in the ARMS for psychosis and may be subserved by structurally altered networks of interconnected cortical and subcortical brain regions in line with the disconnectivity hypothesis of schizophrenia.

1. Introduction

Neuropsychological dysfunction has been regarded as a core feature of schizophrenia as it affects a broad array of cognitive domains very early in the course of the disease (Heinrichs and Zakzanis, 1998) and remains fairly stable over time (Hoff et al., 1992, 1999, 2005; Heaton et al., 2001; Addington et al., 2005). Furthermore, it seems to be largely uncorrelated to psychotic symptoms and antipsychotic treatment, but may be profoundly related to a poor prognosis (Keefe et al., 2004; Hofer et al., 2005; Wölwer et al., 2008; de Gracia Dominguez et al., 2009). Furthermore, a growing body of evidence supports that impaired executive functions (1) constitute a key component within this generalized neuropsychological deficit (Bilder et al., 2000; Joyce et al., 2002; Chan et al., 2006; Lencz et al., 2006), (2) may serve as a risk marker for the subsequent onset of the disease in the at-risk mental state for psychosis (Lencz et al., 2006; Pukrop et al.,

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2007; Riecher-Rössler et al., 2009) and (3) may predict the clinical outcome after the first-episode of the illness (Wölwer et al., 2008).

In particular, the Trail-Making Test B (TMT-B) (Reitan, 1992), which requires the subjects to connect irregularly arranged digits and letters alternately and in ascending order, has repeatedly shown to be a sensitive marker of executive functioning in different neurological (Jurgens et al., 2008; Lima et al., 2008; Johnson et al., 2010) and psychiatric conditions (Beblo et al., 2006; Nakazato et al., 2010; Yatham et al., 2010), including schizophrenia (Hoff et al., 1992; Saykin et al., 1994; Wölwer and Gaebel, 2002). In this regard, the TMT-B may particularly activate the prefrontal cortex (Shibuya-Tayoshi et al., 2007) because the test performance does not only depend on visuomotor integration and working memory as in the "easier" Trail-Making Test A (TMT-A), but requires also the ability to switch between two sets of stimuli (Olivera-Souza et al., 2000). In this regard, the complex executive process activated by the TMT-B may be parsed into a number of more "basic" cognitive functions, like attention, perception and mnemonic processes. It has been suggested that the disruption of these basic functions in schizophrenia relates to structural and functional abnormalities within distributed neural systems (Wölwer and Gaebel, 2002). Thus, the prefrontal cortex may not be exclusively associated with executive dysfunction but may be embedded within a wider network of interconnected temporal, limbic, parietal and subcortical brain structures, as shown by neuroimaging findings in healthy populations (Wager and Smith, 2003) and prodromal or established psychosis (Salgado-Pineda et al., 2003; Antonova et al., 2005; Morey et al., 2005; Rüsch et al., 2007).

Executive deficits have also been described (1) in subjects at a *genetic* risk for the disease (Hans et al., 1999; Faraone et al., 1999; Owens and Johnstone, 2006; Erlenmeyer-Kimling et al., 2000) as well as (2) in individuals in a clinically defined at-risk mental state (ARMS) for psychosis (Hawkins et al., 2004; Brewer et al., 2005; Francey et al., 2005; Niendam et al., 2006; Pukrop et al., 2006; Simon et al., 2007; Blanchard et al., 2010). Furthermore, executive functioning, as measured by the TMT-B, may be particularly affected in the ARMS (Simon et al., 2007; Blanchard et al., 2010) and may further deteriorate over time in those individuals who subsequently convert to full-blown psychosis (Wood et al., 2007). Although volumetric abnormalities within prefrontal, opercular, limbic and paralimbic brain regions have been previously reported in high-risk subjects versus healthy controls (Pantelis et al., 2003; Job et al., 2003, 2005; Borgwardt et al., 2007; Meisenzahl et al., 2008; Koutsouleris et al., 2009b), the neuroanatomy of executive deficits in a clinically defined ARMS have to date not been explored.

Therefore, a neuropsychological test battery was used to measure global cognitive as well as executive performance in ARMS versus HC subjects. We expected executive functions, as measured by the TMT-B, to be specifically impaired beyond global cognitive deficits in the ARMS. Then, we investigated correlations between gray and white matter volumes (GMV/WMV) and executive functioning in ARMS versus healthy control (HC) subjects using whole-brain voxel-based morphometry. Furthermore, we employed the data-driven approach of Rüsch et al. (2007) to detect GM and WM structures throughout the brain that were volumetrically linked to the ventromedial prefrontal cortex, which was previously found to be structurally altered in the high-risk state (Pantelis et al., 2003; Job et al., 2005; Borgwardt et al., 2007; Koutsouleris et al., 2009a) and was now specifically correlated with TMT-B performance in the ARMS group. This structural connectivity analysis aimed at characterizing volumetric networks that were associated with executive dysfunction in the ARMS. We hypothesized that executive dysfunction would relate to a pattern of fronto-temporo-limbic as well as subcortical brain regions previously reported to be altered in the ARMS and schizophrenia.

2. Methods

2.1. Study participants

Forty individuals in a clinically defined ARMS for psychosis and 30 healthy control subjects matched for age, gender and premorbid verbal IQ (Table 2) underwent structural MRI and neuropsychological testing at the Early Detection and Intervention Centre for Mental Crises of the Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University, Germany. The operationalized recruitment criteria have been detailed previously (Meisenzahl et al., 2008; Koutsouleris et al., 2009a,b) and have been widely used by studies investigating the neurobiological and neurocognitive characteristics of the ARMS (see e.g. Ruhrmann et al., 2003, 2010; Schultze-Lutter et al., 2007a; Frommann et al., 2008, 2010; Quednow et al., 2008; Hurlemann et al., 2008). In summary, study inclusion required *either* (1) a positive global functioning & trait marker defined by a $\geq$30 point reduction in the DSM-IV Global Assessment of Functioning Scale *and* a family history of psychotic disorders, *or* a personal history of pre-/perinatal complications, *or* (2) at least 1 positive psychopathological state marker in the basic symptoms (Klosterkötter et al., 2001), attenuated psychotic symptoms (APS) or brief limited intermittent psychotic symptoms (BLIPS) categories (Yung et al., 1998) fulfilling specific duration criteria (Table 1).

Exclusion criteria (Table 1) were assessed for the candidate ARMS and HC individuals by evaluating the personal and familial history using a semi-structured clinical interview as well as the Structured Clinical Interview for DSM-IV (American Psychiatric Association, 1994). A regular follow-up was performed over 4 years in order to detect shifts toward a different ARMS or a transition to psychosis. Subjects meeting the transition criteria (Yung et al., 1998) were diagnosed with a schizophrenia spectrum disorder using the ICD-10 research criteria at transition and after one year. After an average follow-up interval of 3.7 (SD: 1.1) years, information could be obtained from 27 subjects consisting of 11 converters ($n=8$, schizophrenia, $n=3$, schizoaffective psychosis) and 16 nonconverters. Thus, the transition rate was 40.7% in the available follow-up sample. Out of the 13 subjects without follow-up information, 6 could not be contacted or refused to participate, whereas 7 had not completed the follow-up interval. All subjects provided their written informed consent prior to study inclusion. The study was approved by the Local Research Ethics Committee of the Ludwig-Maximilians-University.

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Table 1
Inclusion/exclusion criteria for ARMS and HC subjects. Adopted from Häfner et al. (2004). Abbreviations: APS Attenuated Psychotic Symptoms, BLIPS Brief Limited Intermittent Psychotic Symptoms, GAF Global Assessment of Functioning Score in the Diagnostic and Statistical Manual of Mental Disorders, fourth revision (DSM-IV), American Psychiatric Association (1994).

Inclusion criteria
1. Subjects without APS and/or BLIPS (see below) having one or more of the following basic symptoms appeared first at least 12 months prior to study inclusion and several times per week during the last 3 months. • Thought interferences • Thought perseveration • Thought pressure • Thought blockages • Disturbances of receptive language, either heard or read • Decreased ability to discriminate between ideas and perception, fantasy and true memories • Unstable ideas of reference (subject-centrism) • Derealisation • Visual perception disturbances • Acoustic perception disturbances *And/or* showing a reduction in the GAF score of at least 30 points (within the past year) combined with at least one of the following trait markers • First-degree relative with a lifetime-diagnosis of schizophrenia or a schizophrenia spectrum disorder • Pre- or perinatal complications
2. Subjects having at least one of the following APS within the last three months, appearing several times per week for a period of at least one week • Ideas of reference • Odd beliefs or magical thinking • Unusual perceptual experiences • Odd thinking and speech • Suspiciousness or paranoid ideation
3. Subjects having at least one of the following BLIPS, defined as the appearance of one of the following psychotic symptoms for less than one week (interval between episodes at least one week), resolving spontaneously • Hallucinations • Delusions • Formal thought disorder • Gross disorganised or catatonic behaviour
Exclusion criteria
1. Disease transition as defined by Yung et al. (1998)
2. A past or present diagnosis of schizophrenia spectrum and bipolar disorders, as well as delirium, dementia, amnestic or other cognitive disorders, mental retardation and psychiatric disorders due to a somatic factor, following the DSM-IV criteria
3. Alcohol or drug abuse within three months prior to examination
4. A past or present inflammatory, traumatic or epileptic diseases of the central nervous system
5. Any previous treatment with antipsychotics before MRI and neurocognitive assessment
6. Healthy controls: positive familial history of schizophrenic or affective psychoses in the first-degree relatives

2.2. Neuropsychological testing

A comprehensive neuropsychological test battery was administered to all subjects by trained master-level neuropsychologists (K.PK., J.S., P.D.). The neurocognitive test assessed premorbid verbal IQ (Mehrfachwortschatz-Test (Lehrl, 2005)), processing speed (Digit Symbol Test (Wechsler, 1997), Trail-Making-Test A (Reitan, 1992)), working memory (Digit Span (Wechsler, 1997), Letter Number Span (Gold et al., 1997), Self-Ordered Pointing Task (Petrides, 1995)), verbal learning (Rey Auditory Verbal Learning Test - Immediate and delayed recall, (Lezak, 1995)) and executive functioning (Trail-Making Test B (Reitan, 1992)). Each ARMS subject's performance in these tests was *Z*-transformed based on the mean (SD) data of the HC group.

In order to evaluate whether executive deficits were specifically present in the ARMS versus the HC group beyond a generalized cognitive impairment, we first approximated each subject's global cognitive performance by averaging the respective *Z*-scores of all neurocognitive tests (Simon et al., 2007), except of the TMT-B. Then, group differences regarding time to completion in the TMT-B and global cognitive performance were assessed using *T* tests in SPSS (version 15, SPSS Inc.). The effects of global cognitive performance, age and gender on TMT-B group-level differences were evaluated by conducting an ANCOVA analysis in SPSS with group as the fixed factor, TMT-B as the dependent and global cognitive performance, age and gender as the covariate variables. Due to a significant correlation of TMT-A and TMT-B performance in both study groups, an additional ANCOVA analysis was carried out to evaluate whether the TMT-B group-level differences remained significant after covarying for the effects of TMT-A, age and gender. Finally, the relationships of executive functioning (TMT-B) to global functioning (Global Assessment of Functioning Scale, GAF) and psychopathology (Positive and Negative Symptom Scale, PANSS) were explored using bivariate correlation analysis in SPSS.

Additionally, we explored whether the TMT-B deficits found in the ARMS versus the HC group were driven by the transition (ARMS-T) compared to the non-transition (ARMS-NT) subgroup of our ARMS sample. Due to small subgroup sizes, we employed nonparametric tests to evaluate TMT-B between-group differences (Wilcoxon test). Furthermore, we investigated whether significant TMT-B differences were confounded by global cognitive performance, age and gender or TMT-A performance, age and gender by adjusting forthese effects using partial correlations and repeating the between-group analysis (Table 1). Statistical significance was defined at $P<0.05$.

2.3. MRI data acquisition

MR images were obtained on a 1.5 T Magnetom Vision scanner (Siemens, Erlangen, Germany) using a T1-weighted 3D-MPRAGE sequence (TR, 11.6 ms; TE, 4.9 ms; field of view, 230 mm; matrix, 512×512; 126 contiguous axial slices of 1.5 mm thickness; voxel size,$0.45\times0.45\times1.5$ mm). All scans were carefully checked for scanner artifacts, gross anatomical abnormalities and signs of neurological disease by trained clinical neuroradiologists.

2.4. MRI data preprocessing

MRI scans were preprocessed by means of the VBM8 toolbox (Gaser, 2009) and Statistical Parametric Mapping (SPM8, Wellcome Institute of Neurology, University College London, UK) running under MATLAB 2009b (The MathWorks, Natick, MA, USA). The toolboxextends the unified segmentation model (Ashburner and Friston, 2005) consisting of MRI field intensity inhomogeneity correction, spatial normalization and tissue segmentation at several preprocessing steps in order to further improve the quality of data preprocessing. Initially, the optimized blockwise nonlocal-means filter proposed by Coupé et al. (2006) was applied to the MRI scans using the

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Rician noise adaption introduced in Wiest-Daesslé et al. (2008) to increase the signal-to-noise ratio in the data. Then, an adaptive maximum a posteriori segmentation approach (Rajapakse et al., 1997) extended by partial volume estimation (Manjón et al., 2008) was employed to separate the MRI scans into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF). The segmentation step was finished by applying a spatial constraint to the segmented tissue probability maps based on a hidden Markow Random Field model (Bach Cuadra et al., 2005) that removed isolated voxels which were unlikely to be a member of a certain tissue class and also closed holes in clusters of connected voxels of a certain class, resulting in a higher signal-to-noise ratio of the final tissue probability maps.

Then, the iterative high-dimensional normalization approach provided by the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (Ashburner, 2007, 2009; Klein et al., 2009; Bergouignan et al., 2009) (DARTEL) toolbox was applied to the segmented tissue maps in order to register them to the stereotactic space of the Montreal Neurological Institute (MNI). For this purpose, we employed the IXI templates generated from the structural MRI data of 550 healthy controls (http://fantail.doc.ic.ac.uk), as defined by the default settings of the VBM8 toolbox. The tissue deformations were used to modulate the participants' GM and WM tissue maps in order to compare volumetric differences across groups. Finally, the modulated GM and WM segments were written with an isotropic voxel resolution of 1.5 mm^3 and smoothed with a 5 mm FWHM Gaussian kernel. The considerably improved anatomical overlap of individual tissue maps obtained through the DARTEL normalization allowed the use of a small kernel width, and thus facilitated a high spatial resolution of the cluster-level inference strategy described below.

2.5. Statistical analysis

2.5.1. VBM structure–cognition analysis

Correlations between TMT-B performance and the GMV and WMV tissue maps were explored at the whole-brain level by means of a VBM structure–cognition analysis. For this purpose, two ANCOVA designs were constructed within the framework of the General Linear Model (GLM) (Worsley et al., 1996) that modeled the main effect of group and the interaction with the time to completion in the TMT-B on the smoothed GMV and WMV tissue maps. Possible effects of global GMV and WMV on focal structure–cognition correlations were removed by covarying for these regressors in the respective design matrices.

For each study group (HC/ARMS) and tissue type (GMV/WMV), positive and negative TMT-B correlations were evaluated using the respective T contrasts. Additionally, positive [$TMT-B_{HC} > TMT-B_{ARMS}$] and negative [$TMT-B_{HC} < TMT-B_{ARMS}$] interaction contrasts were defined in order to assess slope differences between the TMT-B correlations of the HC and ARMS groups. Statistical significance was inferred at the cluster-level by assessing the respective SPM{t} images using the nonstationary Random Field Theory (RFT) (Hayasaka et al., 2004). Cluster-level inference strategies have proven to be more sensitive to spatially extended signals compared to voxel-level methods (Poline et al., 1997). This is particularly important in investigations of the ARMS, where the experimental effects are expected to be subtle compared to the established disease. Furthermore, this methodology mitigates the multiple-comparison problem inherent in mass-univariate statistical tests. We employed a previously described, three-step cluster-level inference strategy (Hayasaka et al., 2004; Moorhead et al., 2005; Meisenzahl et al., 2008; Koutsouleris et al., 2009b) that consisted of:

1. Identifying spatially contiguous, potentially significant voxels across the entire brain at a given uncorrected voxel-level threshold (cluster-forming threshold). This threshold was set to $P<0.01$ in order to trade off between sensitivity to cluster extent and separation of maximum voxel results,
2. Correcting the obtained clusters for the varying degree of local smoothness (smoothness nonstationarity) in the VBM data (Ashburner and Friston, 2000) by assessing the resel-per-voxel image generated during parameter estimation (Hayasaka et al., 2004),
3. Applying a family-wise error (FWE) corrected extent threshold of $P<0.05$ (Worsley et al., 1996) to the adjusted clusters sizes, which effectively defined a minimum cluster extent of 2142 mm^3/2662 mm^3 for the GMV/WMV analysis.

Significant clusters were further assessed using Automated Anatomical Labeling (AAL) (Tzourio-Mazoyer et al., 2002) in order to identify within-cluster anatomical regions and to compute the volume (k_{ROI} [vox/mm^3]) and percentage (k_xROI [%]) of significant voxels in each region of the labeled atlas. The anatomical composition of GM clusters was analyzed using the AAL atlas, whereas the WM clusters were examined by means of DTI-81 atlas of the International Consortium for Brain Mapping (Mori et al., 2008).

In a supplementary post-hoc analysis, we extracted the voxel values within the detected suprathreshold clusters using the eigenvariate functionality of SPM8 and averaged them for each cluster and subject. These mean cluster values were adjusted for global GMV and WMV by means of partial correlations and entered a volume-of-interest (VOI) analysis in SPSS that assessed the correlation with TMT-B performance in each study group as well as possible volumetric group-level differences in HC versus ARMS (Supplementary Table 1 and Supplementary Figure 1). Furthermore, we explored whether the observed TMT-B correlations and between-group volume differences were driven by the transition (ARMS-T) compared to the non-transition (ARMS-NT) subgroup of our ARMS sample. Due to small subgroup sizes, we employed nonparametric tests to evaluate TMT-B correlations (Spearman ρ) and volumetric between-group differences (Wilcoxon test). Furthermore, we investigated whether significant TMT-B correlations and volumetric between-group differences were confounded by global cognitive performance, TMT-A performance, age and gender effects (Supplementary Table 2). Therefore, the respective analyses were repeated after adjusting the data for these covariates using partial correlations. Significance of between-group differences and TMT-B correlations was defined at $P<0.05$.

A supplementary VBM analysis was carried out in order to explore the specificity of the neuroanatomical correlates underlying the cognitive set-shifting abilities required by the TMT-B compared to the TMT-A. Therefore, two ANCOVA

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designs were constructed that modeled the main and interaction effects of TMT-A performance on the smoothed GMV and WMC tissue maps. As in the TMT-B analysis, the possible confounding effects of global GMV/WMV were removed by entering these regressors into the respective statistical designs. Joint and differential effects of TMT-A and TMT-B were qualitatively assessed by evaluating the same set of *T* contrasts as described above and visualizing the spatial overlap of significant clusters obtained in the respective contrasts of both analyses (Supplementary Figure 2).

2.5.2. VBM structural connectivity analysis

Furthermore, the present study followed the data-driven approach of Rüsch et al. (2007) and Wilke et al. (2001) to explore the patterns of structural connectivity between the clusters detected in the first step of our analysis. We selected the cluster in the VMPFC, which was characterized by a negative correlation between TMT-B and GMV in the ARMS group, as the primary seed region for the VBM connectivity analysis. The rationale for this choice was (1) the consistent involvement of this cortical area in the ARMS for psychosis (Pantelis et al., 2003; Job et al., 2005; Borgwardt et al., 2007; Koutsouleris et al., 2009a) and (2) its rich connectivity to prefrontal, limbic, temporal, parietal and subcortical brain regions (Petrides and Pandya, 1988; Siwek and Pandya, 1991; Morecraft et al., 1992; Ray and Price, 1993; Rolls and Baylis, 1994) suggesting an important integrative role of the VMPFC in cognitive and emotional processes (Damasio et al., 1996).

As described above, we extracted the vector of the study participants' mean voxel values from the VMPFC cluster (Supplementary Figure 1) and entered it as a regressor into two ANCOVA designs that modeled its interaction with the main effect of group on the smoothed GMV/WMV tissue maps, while covarying for the effects of global GMV/WMV. We employed the identical statistical inference strategy that had been used in the VBM structure–cognition analysis to test for suprathreshold clusters of positive/negative correlations between the VMPFC seed cluster and GMV/WMV in each study group. Thus, FWE- and nonstationarity-corrected cluster extent thresholds were defined at 1994 mm^3/2757 mm^3 for the respective GMV/WMV models. Finally, significant clusters were overlaid on the mean T1 image obtained through averaging the normalized, skull-stripped T1 scans of all study participants (Fig. 3).

3. Results

3.1. Neurocognitive performance

The HC and the ARMS groups differed significantly in their TMT-B ($z=-1.6$ (SD = 1.1), $T=4.55$, $P<0.001$) and general cognitive performance ($z=-0.93$ (1.8), $T=4.76$, $P<0.001$, Table 2). The TMT-B difference remained significant after covarying for the effects of general cognitive performance, age and gender ($F=5.16$, $P=0.026$, Table 2). TMT-B and TMT-A scores were significantly correlated across ($r=.54$, $P<0.001$) and within groups: $r_{HC}=.36$, $P=0.05$; $r_{ARMS}=.54$, $P<0.001$. The TMT-B difference remained significant after covarying for the effects of TMT-A, age and gender ($F=11.7$, $P<0.001$). Furthermore, the ARMS subjects' TMT-B scores were not significantly associated with the GAF score, the total PANSS score or the PANSS subscale scores ($r_{GAF}=-.19$, $r_{PANSS\ total}=-.11$, $r_{PANSS\ negative}=-.16$, $r_{PANSS\ positive}=-.04$, $r_{PANSS\ general}=-.11$).

The ARMS-NT and ARMS-T subgroups differed significantly in the TMT-B ($z_{ARMS-NT}=-1.6$ (2.0), $z_{ARMS-T}=-2.6$ (1.3), Wilcoxon's $W=113$, $P=0.043$), but not in the TMT-A performance ($z_{ARMS-NT}=-0.3$ (1.7), $z_{ARMS-T}=-0.8$ (1.4), $W=131$, $P=0.272$) or general cognitive performance ($z_{ARMS-NT}=-0.7$ (1.0), $z_{ARMS-T}=-1.3$ (1.3), $W=129$, $P=0.231$). The significant TMT-B group-level difference did not survive the statistical correction for global cognitive performance, age and gender ($W=144$, $P=0.645$) or TMT-A, age and gender ($W=148$, $P=0.790$).

3.2. VBM brain-cognition analysis

3.2.1. TMT-B correlations in the HC group (Table 3, Fig. 1, Supplementary Tables 1 & 2, Supplementary Figure 1)

Positive correlations between time to completion in the TMT-B and GMV were detected in two clusters (cluster 1 (right insula): $P_{FWE}=0.014$, $k_c=846$ voxels; cluster 2 (left insula): $P_{FWE}=0.004$, $k_c=1069$), which covered the anterior portion of the insular cortices, bilaterally, and extended to the inferior frontal gyrus, pars orbitalis, on the right hemisphere. No negative correlations between TMT-B performance and GMV were observed. Furthermore, no correlations between TMT-B performance and WMV were detected.

The post-hoc VOI analysis verified a positive correlation of both mean cluster values with TMT-B performance in the HC group (cluster 1: Pearson's $r=0.82$, $P<0.001$; cluster 2: $r=0.76$, $P<0.001$), but not in the ARMS group (cluster 1: $r=-0.19$, $P=0.217$; cluster 2: $r=-0.15$, $P=0.361$). These correlations remained significant after controlling for the effects of global cognitive performance, age and gender or TMT-A score, age and gender. No significant volumetric group differences were identified in these two clusters.

3.2.2. TMT-B correlations in the ARMS group (Table 3, Fig. 2, Supplementary Tables 1 & 2, Supplementary Figure 1)

Positive correlations between TMT-B and GMV were detected in two clusters within the cerebellar cortex and the vermis. The first cluster ($P_{FWE}<0.001$, $k_c=3508$) covered the vermal GMV as well as portions of the right cerebellar hemisphere, whereas the second cluster ($P_{FWE}=0.002$, $k_c=1032$) was confined to the left cerebellar cortex. Negative correlations between TMT-B performance and GMV were localized in a cluster that symmetrically occupied parts of the ventromedial prefrontal cortex (VMPFC) (cluster 1: $P_{FWE}<0.001$, $k_c=4828$). Furthermore, negative correlations between TMT-B and WMV were detected in a cluster that extended from the genu of the corpus callosum to the radiatio anterior, bilaterally (cluster 1: $P_{FWE}<0.001$, $k_c=2583$).

The post-hoc VOI analysis confirmed the correlations between the ARMS individuals' mean cluster values and their TMT-B score (positive correlations with GMV: cluster 1: $r=0.556$, $P<0.001$; cluster 2: $r=0.469$, $P=0.002$, negative correlations with GMV: cluster 1: $r=-0.682$, $P<0.001$, negative correlations with WMV: cluster 1: $r=-0.631$, $P<0.001$) as well as the absence of significant structure–cognition correlations in these brain regions for the HC group. These associations remained significant after adjusting the cluster values for the effects of global cognitive performance,

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Table 2
Analysis of sociodemographic, clinical, global anatomical and neurocognitive variables. Abbreviations: ARMS At-Risk Mental State for psychosis, ARMS-NT non-conversion subgroup, ARMS-T conversion subgroup, GAF Global Assessment of Functioning, HC Healthy Control subjects, PANSS Positive and Negative Symptom Scale, *T* Student's *t* test value, *W* Wilcoxon's test value, χ^2 Pearson χ^2 value. The TMT performances of the ARMS subjects were *z*-transformed using the mean (SD) of the respective scores in the HC group. All *P* values are two-sided and exact in the nonparametric tests.

	HC	ARMS	T/χ^2	*P*	ARMS-NT	ARMS-T	W/χ^2	*P*
Sociodemographic variables								
N	30	40			16	11		
Age: mean (SD) [years]	26.0 (2.7)	24.5 (5.9)	1.51	n.s.	26.0 (6.8)	21.6 (3.3)	124.0	n.s.
Gender	18/12	27/13		n.s.	11/5	9/2	0.58	n.s.
Male/female (%)	(60/40)	(67.5/32.5)			(68.8/31.3)	(81.8/18.2)		
Handedness	29/1/0	33/4/3	0.42	n.s.	12/3/1	11/0/0	3.23	n.s.
Right/left/ambidextruous (%)	(96.7/3.3/0)	(82.5/10.0/7.5)			(75.0/18.8/6.3)	(100/0/0)		
School education: mean (SD) [years]	12.4 (1.2)	11.9 (1.2)	1.87	n.s.	11.8 (1.3)	11.6 (1.2)	146.5	n.s
Clinical variables								
No. (%) of first-degree relatives with schizophrenic psychoses	–	4/40 (10.0)						
No. (%) of first-degree relatives with affective psychoses	–	6/40 (15.0)						
GAF score: mean (SD)	–	58.6 (11.6)			59.1 (11.9)	60.0 (15.4)	119.0	n.s.
PANSS total score: mean (SD)	–	60.1 (18.6)			48.2 (9.1)	65.3 (21.3)	105.5	<0.05
PANSS positive score: mean (SD)	–	12.2 (4.2)			9.6 (2.2)	14.5 (3.8)	100.5	<0.001
PANSS negative score: mean (SD)	–	15.7 (7.9)			11.2 (4.3)	18.5 (9.4)	100.0	<0.001
PANSS general score: mean (SD)	–	32.2 (9.4)			27.5 (5.5)	32.3 (11.2)	118.0	n.s.
MADRS score: mean (SD)	–	15.2 (8.9)			16.0 (4.8)	6.4 (3.5)	31.5	<0.001
Global anatomical parameters [ml]								
Gray matter volume: mean (SD)	610.5 (36.9)	635.1 (63.3)	−2.03	<0.05 [a]	619.3 (58.7)	676.1 (57.7)	177.0	<0.05 [a]
White matter volume: mean (SD)	613 (63.4)	621.8 (70.3)	−0.50	n.s.	625.0 (83.0)	629.6 (54.9)	221.0	n.s.
Cerebrospinal fluid volume: mean (SD)	199.8 (22.9)	199.5 (28.1)	0.04	n.s.	199.0 (34.2)	200.5 (22.0)	219.0	n.s
Total intracranial volume: mean (SD)	1423.9 (106.7)	1456.4 (126.8)	−1.13	n.s.	1443.0 (144.2)	1506.0 (102.1)	194.0	n.s.
Neurocognitive performance	HC_{raw}	$ARMS_{raw/Z}$	*T* (*F*)	*P*	$ARMS\text{-}NT_{raw/Z}$	$ARMS\text{-}T_{raw/Z}$	*W*	*P*
Trail-Making Test B: mean (SD)	48.0 (13.3)	68.6 (24.2)	−4.55	<0.001	68.4 (27.0)	81.9 (17.3)	113.0	0.043
		−1.6 (1.8)			−1.6 (2.0)	−2.6 (1.3)		
Statistically corrected for global cognitive performance, age & gender			5.16	0.026			144.0	n.s.
Statistically corrected for TMT-A performance, age & gender			11.7	<0.001			148.0	n.s.
Trail-Making Test A: mean (SD)	24.8 (5.6)	28.0 (8.4)	−1.95	n.s.	26.3 (9.3)	29.1 (7.6)	131.0	n.s.
		−0.6 (1.8)			−0.3 (1.7)	−0.8 (1.4)		
Global cognitive performance: mean (SD)	–	–	4.76	<0.001			129.0	n.s.
		−0.93 (1.1)						
Premorbid verbal IQ: mean (SD)	109.3 (8.6)	106.9 (14.4)	0.86	n.s.	111.3 (14.1)	104.2 (17.3)	129.5	n.s.

[a] Not significant after statistically correcting for the effects of age and gender.

age and gender or TMT-A score, age and gender. No significant volumetric between-group differences were observed for any of these clusters.

Positive correlations between TMT-B and cerebellar GMV were partly driven by the non-converters (cluster 1: Spearman's $\rho = 0.545$, $P = 0.029$; cluster 2: $\rho = 0.472$, $P = 0.065$). However, the significant correlation between the cerebellar GMV cluster 1 and TMT-B disappeared after controlling for cognitive performance/TMT-A score, age and gender. No significant TMT-B correlations were observed in the ARMS-T subgroup for any of the suprathreshold clusters. Volumetric differences between ARMS-NT and ARMS-T subgroups were detected in the VMPFC cluster ($W = 108$; $P = 0.023$), which, however, did not survive the statistical correction for global cognitive performance, age and gender ($W = 129$, $P = 0.231$) or TMT-A score, age and gender ($W = 122$, $P = 0.121$).

3.2.3. Interaction contrasts: $[TMT - B_{HC} > TMT - B_{ARMS}]$ and $[TMT - B_{HC} < TMT - B_{ARMS}]$

The positive interaction contrast $[TMT - B_{HC} > TMT - B_{ARMS}]$ revealed a set of suprathreshold GMV clusters that almost completely overlapped with the clusters of positive correlations between TMT-B and GMV found in the HC group (Fig. 1A & B). No significant GMV clusters were detected in the negative interaction contrast $[TMT - B_{HC} < TMT - B_{ARMS}]$. Furthermore, no suprathreshold WMV clusters were identified using the positive and negative interaction contrasts.

3.2.4. Supplementary VBM analysis (Supplementary Figure 2)

No positive or negative correlations between time to completion in the TMT-A and GMV/WMV were detected in the HC group. In the ARMS group, a region of spatial overlap

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Table 3
Anatomical localization of clusters. The table lists ROIs where more than 5% of within-ROI voxels were covered by clusters. Headers: Lat Laterality (L left, R right), ROI [vox] size of region-of-interest in voxels, ROI [mm^3] size of region-of-interest in mm^3, k_{ROI} [vox] portion of ROI covered by cluster in voxels, k_{ROI} [mm^3] portion of ROI covered by cluster in mm^3, k_{ROI} [%] percentage of ROI covered by cluster. Anatomical abbreviations: Ant anterior, Inf inferior, Orb orbital.

Anatomical region	Lat	ROI [vox]	ROI [mm^3]	k_{ROI} [vox]	k_{ROI} [mm^3]	k_{ROI} [%]
Gray matter						
[HC, positive correlations with TMT-B]						
Insula	L	4326	14600	810	2734	18.7
Insula	R	4214	14222	457	1542	10.8
Frontal Inf Orb	R	4008	13527	232	783	5.8
[ARMS, positive correlations with TMT-B]						
Vermis 8		531	1792	125	422	23.5
Vermis 7		459	1549	65	219	14.2
Cerebellum 8	R	5420	18292	740	2498	13.7
Cerebellum 7b	R	1270	4286	166	560	13.1
Cerebellum Crus2	R	5081	17148	640	2160	12.6
Cerebellum Crus2	L	4528	15282	558	1883	12.3
Cerebellum Crus1	R	6216	20979	671	2265	10.8
Cerebellum Crus1	L	6130	20689	444	1498	7.2
Cerebellum 9	R	1942	6554	131	442	6.8
[ARMS, negative correlations with TMT-B]						
Rectus	L	2056	6939	380	1282	18.5
Rectus	R	1813	6119	205	692	11.3
White matter						
[ARMS, negative correlations with TMT-B]						
Genu of corpus callosum		2674	9025	1451	4897	54.3
Ant corona radiata	L	2035	6868	591	1995	29.0
Ant corona radiata	R	2035	6868	272	918	13.4

was detected within the left cerebellar hemisphere after superimposing the clusters of positive TMT-A/GMV correlations on the respective TMT-B clusters. Similarly, a spatial overlap was identified within the VMPFC and the genu of corpus callosum when superimposing the clusters of negative correlations between TMT-A and GMV/WMV on the respective TMT-B clusters. Furthermore, specific negative TMT-A correlations were observed in the left caudate nucleus and the medial occipital cortex. No negative TMT-A associations were detected in the frontal and orbitofrontal WMV.

3.3. VBM structural connectivity analysis

The structural connectivity pattern in the HC group consisted of 5 GMV clusters that correlated positively with the VMPFC seed cluster and were located in the orbitofrontal, as well as the medial, inferior and lateral temporal lobe regions (Fig. 3). These volumetric associations covered (1) parts of the parahippocampal cortex, bilaterally, with extensions to hippocampus and amygdala, as well as (2) the temporal poles with extensions to the superior temporal sulcus, the fusiform and lingual gyri, bilaterally. Expectedly, a strong positive GMV correlation was observed within and in the direct neighborhood of the seed cluster. Furthermore, the structural connectivity pattern included also negative volumetric correlations between the seed cluster and GMV, which were confined to left cerebellar hemisphere and the medial occipital cortex. No suprathreshold clusters of positive/negative volumetric correlations with WMV were found in the HC group.

The structural connectivity pattern in the ARMS group consisted of positive GMV correlations with the VMPFC seed cluster that involved (1) the neighborhood of the seed cluster, with extensions to the olfactory, orbitofrontal and subgenual anterior cingulate cortex, (2) the left middle temporal gyrus and (3) the left dorsolateral prefrontal cortex (Fig. 3). Negative correlations were detected in (1) the cerebellar hemispheres, bilaterally and the vermis, (2) the right calcarine sulcus, as well as (3) within the right paracentral lobule covering primarily the supplementary motor area. Moreover, the seed cluster's connectivity involved also positive correlations within a bilateral WM cluster that extended from the radiatio anterior over the rostrum and genu to the body of the corpus callosum.

4. Discussion

We detected possible neuroanatomical underpinnings of executive deficits in neuroleptic-naive subjects with a clinically defined at-risk mental state for psychosis compared to a group of healthy volunteers matched for age, gender and premorbid verbal IQ using whole-brain, rater-independent voxel-based morphometry. In this regard, our sample's sociodemographic and clinical characteristics (Table 2) were comparable to previous investigations employing the combined basic symptoms-UHR approach to study neurocognitive and/or neuroanatomical abnormalities in the ARMS of psychosis (Hurlemann et al., 2008; Schultze-Lutter et al., 2007b; Pukrop et al., 2006, 2007). Furthermore, the transition rate of 41% in the subgroup of 27 ARMS subjects with available clinical follow-up information is in line with the initial findings from the PACE clinic in Australia (Yung et al., 2003, 2004), the TOPP clinic in Norway (Larsen, 2002) or the North American Prodrome Longitudinal Study (Miller et al., 2002; Cannon et al., 2008), supporting that our sample is representative of an elevated vulnerability for developing a schizophrenia spectrum psychosis.

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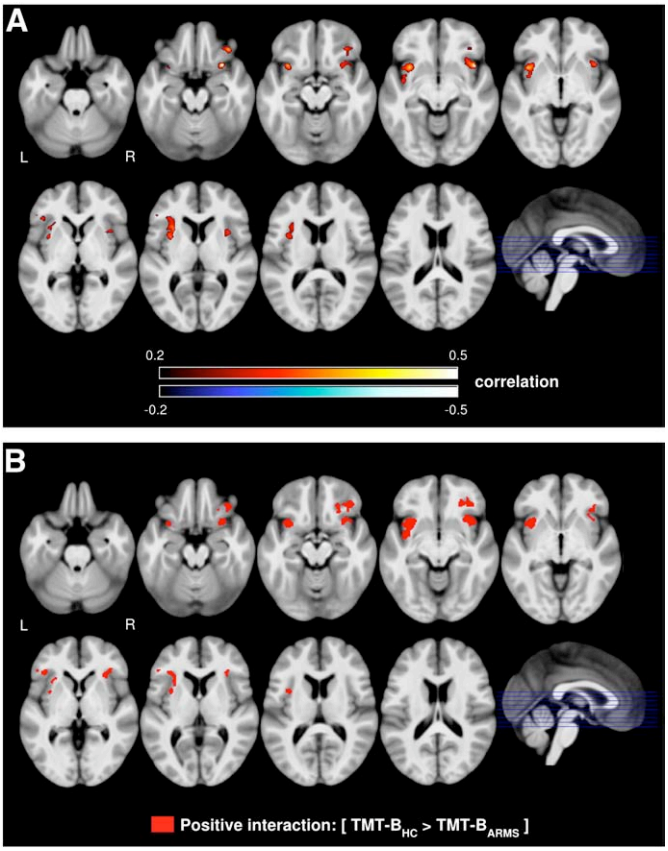

Fig. 1. Structure–cognition correlations of the Trail-Making Test B in the healthy control group. Part A: Significant clusters of positive (warm color scale) and negative (cool color scale) correlations between time to completion in the TMT-B and GMV as well as WMV were overlaid on the average normalized and skull-stripped T1-image obtained from all study participants using the software package MRIcron (C. Rohrden, http://www.sph.sc.edu/comd/rorden/mricron/). Part B: Similarly, significant clusters of the positive interaction contrast [TMT − B_{HC} > TMT − B_{ARMS}] were visualized using MRIcron. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4.1. Executive dysfunction in the ARMS for psychosis

The prolongated time to completion in our ARMS subjects' TMT-B performance agrees with neuropsychological studies of high-risk subjects (Fis et al., 2008; Hawkins et al., 2004; Brewer et al., 2005; Pukrop et al., 2007; Wood et al., 2007), healthy relatives of schizophrenic patients (Franke et al., 1993), subjects diagnosed with schizotypal personality disorder (Trestman et al., 1995) and schizophrenia (Hoff et al., 1992; Saykin et al., 1994; Wölwer and Gaebel, 2002; Wölwer et al., 2008). These studies suggest that impairments in cognitive set-shifting, as measured by the TMT-B, may be regarded as a trait characteristic or even vulnerability marker of schizophrenia spectrum psychosis as they appear very early in the course of the illness and are associated with a genetic risk for the disease (Franke et al., 1993; Pukrop et al., 2007; Fis et al., 2008). In this context, the missing association between the TMT-B performance of our ARMS group and the obtained psychopathological data may indeed support that the TMT-B captures a neurocognitive trait that is linked to an elevated susceptibility for the disease.

Furthermore, the significant TMT-group level differences obtained after correction for global cognitive performance or TMT-A performance (Table 2) confirmed the hypothesized specificity of executive impairment in the ARMS for psychosis by showing that deficits in cognitive set-shifting (1) were superimposed on a profile of generalized cognitive dysfunction in keeping with previous findings in schizophrenic patients compared to HC (Bilder et al., 2000; Joyce et al., 2002; Chan et al., 2006; Lencz et al., 2006) and (2) characterized the ARMS beyond deficiencies of visuomotor coordination and working memory, as recently shown by Simon et al. (2007) and Blanchard et al. (2010). Moreover, recent studies suggested that cognitive set-shifting deficits may have prognostic validity as they seem to be more pronounced in clinically defined ultra-high risk ARMS subjects who suffer from APS and/or BLIPS (Pukrop et al., 2007) and because they may further deteriorate in those ARMS individuals who subsequently go on to develop a full-blown psychotic disorder (Wood et al., 2007). Our finding that ARMS individuals with a subsequent transition to psychosis had pronounced deficits in the TMT-B compared to the non-conversion group may be consistent with these studies (Table 2). However, our ARMS-T versus ARMS-NT analyses have to be interpreted with great caution due to the small sample sizes and nonsignificant findings obtained after statistically correcting for global cognitive/TMT-A performance, age and gender effects.

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Time to completion in the TMT-B may only provide a relatively crude measure of executive dysfunction because on the one hand it relies on a number of more basic neurocognitive functions including attentive, visual, motor and mnemonic processes and on the other hand it depends on the temporal organization and integration of these subprocesses. To further disentangle the interactions of these cognitive functions, Wölwer and Gaebel (2002) recorded hand and eye movements of healthy controls and patients with schizophrenia and major depression during the administration of the TMT-A und TMT-B, which facilitated the detailed examination of planning, acting and resting periods during these tests. The authors found that particularly the poorer TMT-B performance of schizophrenic patients was related to a "strategic problem" in the temporal sequencing of behavior. Under the high cognitive load of the TMT-B, which demands the maintenance and manipulation of alphabetical and numeric task sequences (Kortte et al., 2002; Arbuthnott and Frank, 2000), this deficiency lead the patients to switch to a "serial mode" of information processing instead of using the parallel execution mode available to the healthy controls, thus causing a prolongation of the overall performance process.

The authors suggested that these cognitive deficits were not only subserved by the prefrontal cortices, but were related to a dysfunction within a network of cortical and subcortical structures. Indeed, using functional MRI, Zakzanis et al. (2005) showed that the TMT-B-induced brain activations of healthy volunteers were not confined to the prefrontal cortex but rather involved a distributed pattern of brain regions including the dorsolateral and medial prefrontal cortices, the insula, the middle and superior temporal cortices as well as the SMA. In keeping with this finding, using positron emission tomography, Horacek et al. (2006) found that resting brain hypometabolism in the ventromedial and dorsolateral cortex and widespread hypermetabolism in limbic, medial parietal, temporal, occipital and subcortical brain regions predicted time to complete the TMT-B in schizophrenic patients but not healthy controls. These studies support that the TMT-B sensitively measures the integrity of a distributed neural circuitry, which generates and integrates different cognitive functions involved in this complex task, including cognitive set-shifting, visuomotor coordination and working memory.

4.2. Neuroanatomical correlates of executive dysfunction in the ARMS for psychosis

To the best of our knowledge, this is the first study to report on neuroanatomical correlates of executive impairment in

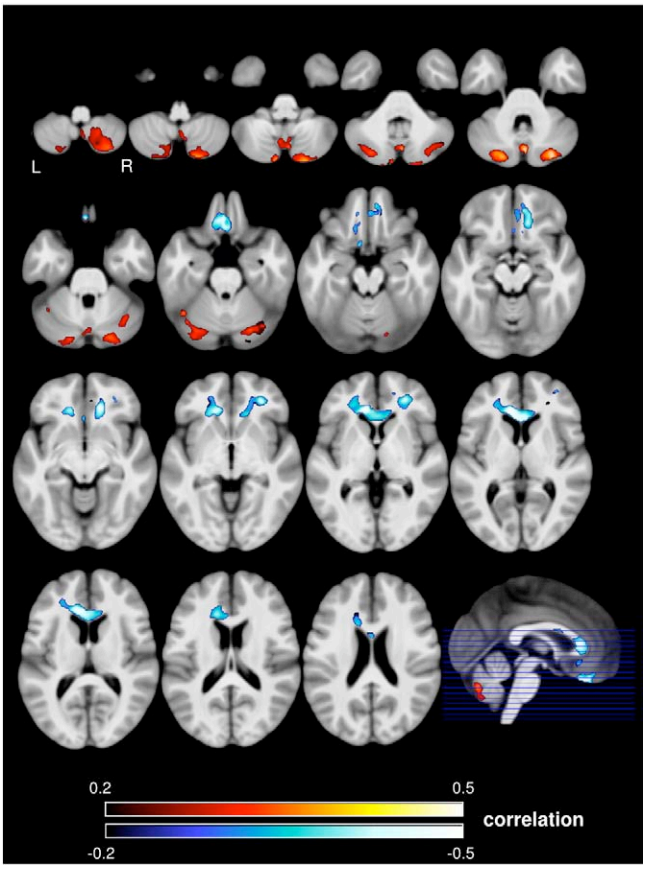

Fig. 2. Structure–cognition correlations of the Trail-Making Test B in the ARMS group. Significant clusters of positive (warm color scale) and negative (cool color scale) correlations between time to completion in the TMT-B and GMV as well as WMV were overlaid on the average normalized and skull-stripped T1-image obtained from all study participants using the software package MRIcron (C. Rohrden, http://www.sph.sc.edu/comd/rorden/mricron/). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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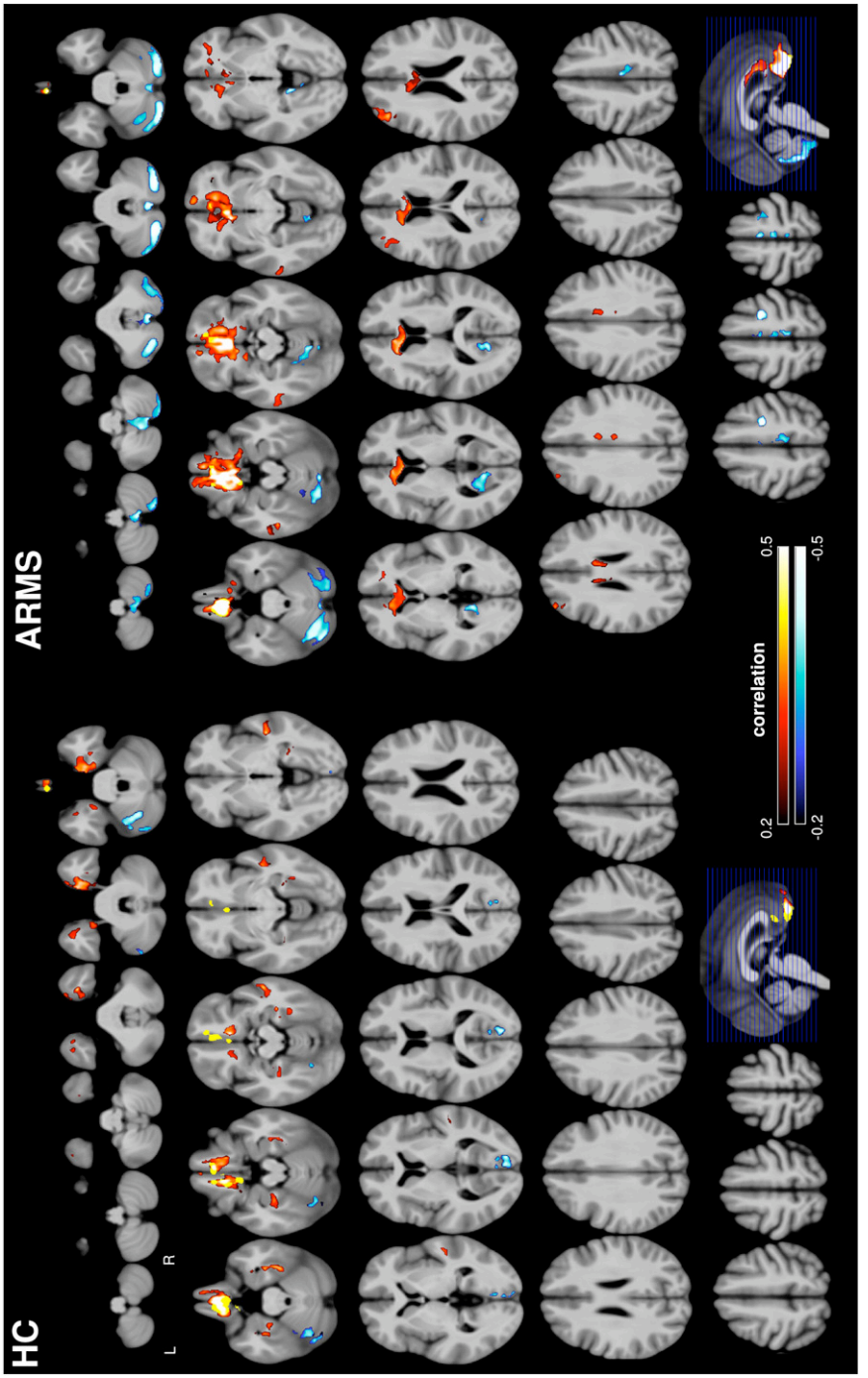

Fig. 3. Structural connectivity analysis of the VMPFC cluster in the HC and ARMS groups. Significant clusters of positive (warm color scale) and negative (cool color scale) correlations between the study participants' average volumes in the VMPFC cluster obtained in the first analysis step and GMV as well as WMV were overlaid on the average normalized and skull-stripped T1-image obtained from all study participants using the software package MRIcron (C. Rohrden, http://www.sph.sc.edu/comd/rorden/mricron/). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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subjects with a clinical ARMS for psychosis as defined by established and operationalized high-risk criteria. Our healthy volunteers showed strong positive TMT-B correlations in the GMV of the anterior insular cortices, which extended to the pars orbitalis of the right inferior frontal gyrus. These structure–cognition associations were disrupted in the ARMS group. In contrast, the VBM analysis revealed that the ARMS individuals' prolongated time to completion in the TMT-B was *negatively* correlated with ventromedial prefrontal GMV and fronto-callosal WMV, as well as *positively* correlated with cerebellar GMV. These associations between brain structure and TMT-B performance remained significant after controlling for global cognitive/TMT-A performance, age and gender effects (Supplementary Table 2), suggesting that these associations represent specific neuroanatomical correlates of cognitive set-shifting impairments. This hypothesis is further supported by (1) the *negative* findings of the TMT-A correlation analysis in the HC subjects and (2) the TMT-B correlations within the cerebellar GMV and prefrontal GMV/ WMV of the ARMS group, which were spatially more extended than the respective TMT-A clusters (Supplementary Figure 2).

In line with the VBM structure–cognition analyses, the structural connectivity analysis of the VMPFC seed cluster revealed almost non-overlapping patterns of GMV and WMV associations in ARMS compared to HC subjects. The HC group's connectivity pattern consisted of positive volumetric correlations with the temporo-limbic GMV and circumscribed negative correlations within the left cerebellum and the right cuneus. In particular, the volumetric connectivity between the ventromedial prefrontal and medial-inferior temporal cortices could not be traced in the ARMS group. In contrast, the ARMS subjects' connectivity pattern involved positive volumetric correlations with the left middle temporal and dorsolateral prefrontal cortex as well as with fronto-callosal white matter tracts. Negative correlations were more extended compared to HC and covered the cerebellum, the left calcarine sulcus and the right SMA.

This ARMS-specific volumetric network showed a considerable spatial overlap with neuroanatomical abnormalities reported by recent studies of genetically or clinically defined at-risk subjects (Pantelis et al., 2003; Job et al., 2005; Borgwardt et al., 2007, 2008; Meisenzahl et al., 2008; Koutsouleris et al., 2009b) and schizophrenic patients (see Pantelis et al., 2005; Honea et al., 2005, for review). Moreover, altered brain-cognition associations have been previously described in established psychosis affecting particularly prefrontal structures, including attenuated correlations between decision-making, cognitive set shifting and orbitofrontal GMV (Nakamura et al., 2008; Premkumar et al., 2008) as well as positive correlations between (1) frontal WMV and cognitive flexibility (Sanfilipo et al., 2002), (2) fronto-callosal white matter integrity and executive functioning (Pérez-Iglesias et al., 2010), and (3) DLPFC volume and executive impairment (Gur et al., 2000; Rüsch et al., 2007; Bonilha et al., 2008). Furthermore, the involvement of the SMA and the cerebellum observed in the present study is in keeping with the investigation of Exner et al. (2006) that reported associations between SMA volume and motor sequence learning in first-episode schizophrenia, as well as with Segarra et al. (2008) who found cerebellar GMV and WMV to be specifically associated with cognitive flexibility and working memory in schizophrenic patients. These links between executive deficits and neuroanatomical data support the "misconnection syndrome" hypothesis (Crow, 1998; Andreasen et al., 1998; Spalletta et al., 2003) This model posits that the disruption of neural circuitry connecting the prefrontal cortex to further cortical and subcortical brain structures causes a fragmentation of cognitive processes leading subsequently to the diverse behavioral phenotypes of schizophrenia.

Our data is in line with this hypothesis as the structural connectivity between the VMPFC and the temporo-limbic brain regions found in our HC individuals could not be traced in the ARMS group. Due to its dense structural and functional connectivity to limbic and paralimbic structures (amygdala, hippocampus, parahippocampus, insular and anterior cingulate cortices), the VMPFC has been regarded as a core structure involved in emotional decision making. According to Damasio's somatic marker hypothesis (Damasio et al., 1996), it may integrate cognitive processes with stored reinforcing stimuli that had been associated with affective experiences ("somatic markers"), thus allowing to *intuitively* choose among conflicting alternatives during decision-making tasks. In the context of this hypothesis and the aforementioned studies of Zakzanis et al. (2005) and Horacek et al. (2006), our data may suggest that impaired cognitive set-shifting in the ARMS is subserved (1) by a *reduced* structural connectivity in the "decision-making" network involving the ventromedial prefrontal cortex, the limbic and paralimbic brain regions, as well as (2) by an *increased* structural connectivity within a network related to visuomotor control that comprised the dorsolateral and ventromedial prefrontal cortex, cerebellum, cuneus and SMA. In agreement with the interpretation of Rüsch et al. (2007), we may speculate that the negative correlations between VMPFC and cerebellum, cuneus and SMA reflect an *adaptive* process that compensates for the alterations in the prefronto-temporo-limbic decision network. Thus, the continuous recruitment of such compensatory structures may lead to an augmentation of local GMV, e.g. through an increase in synaptic density, and therefore to an inverse volumetric association. This hypothesis may be further supported by our conversion versus non-conversion analysis that showed (1) that the ARMS-specific volumetric correlations in the cerebellum were partly driven by the ARMS-NT compared to the ARMS-T subjects and (2) that the VMPFC volume was reduced in the ARMS-T versus the ARMS-NT individuals. These findings, although preliminary and nonsignificant after correcting for global cognitive/TMT-A performance, age and gender, may point to a *deficient* adaptive process in those who ultimately develop a frank psychotic disorder. This hypothesis should be further investigated in future studies analyzing neurocognitive and neuroanatomical data of significantly larger outcome groups.

Considerable inconsistencies exist in the schizophrenia literature regarding the direction of correlations between brain volumes and executive impairment. In keeping with the present study, Rüsch et al. (2007) identified a reduction of prefrontal GMV in schizophrenic patients with poor compared to good executive functioning. The structural network associated with this primary brain-cognition substrate consisted of positive (anterior cingulate, orbitorfrontal and parietal cortices) and negative volumetric correlations

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(parahippocampal gyrus, thalamus, cerebellum). In contrast to these findings, Segarra et al. (2008) observed a positive correlation between cerebellar GMV/WMV and executive functioning in established psychosis, whereas Szeszko et al. (2003) reported that cerebellar volume and neurocognition were uncorrelated in their schizophrenia sample. These inconsistencies might be due to divergent methodological strategies and clinical differences between the examined schizophrenia samples (e.g. disease stage, chronicity and medication effects). In particular, the phase of disease transition as well as the first years of established psychosis may be characterized by dynamic structural brain changes as reported by recent cross-sectional and longitudinal studies of high-risk and first-episode populations (Phillips et al., 2002; Pantelis et al., 2003; Job et al., 2002, 2003, 2005; Whitford et al., 2006; Borgwardt et al., 2007, 2008; Koutsouleris et al., 2009b). Thus, not only volumetric reductions, but also volumetric increments have been observed within brain regions that considerably overlap with the ARMS-specific brain-cognition pattern observed in the present study (Borgwardt et al., 2007), suggesting that these neuroanatomical alterations, and hence also structure–cognition covariance patterns, may evolve on non-linear trajectories during the early phases of psychosis. Future studies that prospectively combine structural and neurocognitive measurements may provide a deeper insight into course of these trajectories.

To our knowledge, this is the first report of brain-cognition relationships in a clinically defined ARMS for psychosis using a whole-brain, state-of-the-art VBM procedure. In summary, we identified executive impairments in neuroleptic-naive ARMS subjects compared to matched HC that (1) related to a volumetric pattern covering mainly prefrontal, premotor, occipital and cerebellar brain regions and (2) were linked to an attenuated structural connectivity between the prefrontal and limbic–paralimbic cortices. The spatial overlap between these patterns and previously described neuroanatomical abnormalities in early psychosis points to a pathophysiological process that impacts on the integrity of a distributed neural circuitry, and thus causes the fragmentation of fluid cognitive processing in line with the disconnectivity hypothesis of schizophrenia.

Supplementary data to this article can be found online at doi:10.1016/j.schres.2010.08.026.

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Contributors

Author Nikolaos Koutsouleris participated in the recruitment of ARMS subjects and the acquisition of MRI, clinical and neurocognitive data. He performed the data processing and statistical analysis and wrote the manuscript.

Author Katja Patschurek-Kliche participated in the collection of neuropsychological & MRI data, in the evaluation and discussion of the results and the writing of the manuscript.

Author Johanna Scheuerecker participated in the collection of neuropsychological & MRI data, in the evaluation and discussion of the results.

Author Petra Decker participated in the recruitment of the ARMS subjects, the acquisition of clinical and neuropsychological data.

Author Ronald Bottlender participated in the design of the study, was responsible for the recruitment of ARMS subjects and the acquisition of clinical data, and was involved in the evaluation of results and the writing of the manuscript.

Author Gisela Schmitt participated in the acquisition of the data, the evaluation of results.

Author Dan Rujescu participated the acquisition of clinical and neuropsychological data and the writing of the manuscript.

Author Ina Giegling participated the acquisition of clinical and neuropsychological data and the writing of the manuscript.

Author Christian Gaser participated in the evaluation and discussion of the results and the writing of the manuscript.

Author Maximilian Reiser participated in the acquisition of MRI data and the writing of the manuscript.

Author Hans-Jürgen Möller supervised the evaluation and discussion of scientific results and participated in the writing of the manuscript.

Author Eva Meisenzahl designed the study, participated in the collection of clinical and MRI data, evaluated the results of statistical analysis and was involved in the writing of the manuscript.

Conflict of interest

No conflict of interest exists for any of the authors.

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