Multivariate Patterns of Brain–Cognition Associations Relating to Vulnerability and Clinical Outcome in the At-Risk Mental States for Psychosis

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Abstract: *Background*: Neuropsychological deficits are a core feature of established psychosis and have been previously linked to fronto-temporo-limbic brain alterations. Both neurocognitive and neuroanatomical abnormalities characterize clinical at-risk mental states (ARMS) for psychosis. However, structure–cognition relationships in the ARMS have not been directly explored using multivariate neuroimaging techniques. *Methods*: Voxel-based morphometry and partial least squares were employed to study system-level covariance patterns between whole-brain morphological data and processing speed, working memory, verbal learning/IQ, and executive functions in 40 ARMS subjects and 30 healthy controls (HC). The detected structure–cognition covariance patterns were tested for significance and reliability using non-parametric permutation and bootstrap resampling. *Results*: We identified ARMS-specific covariance patterns that described a generalized association of neurocognitive measures with predominantly prefronto-temporo-limbic and subcortical structures as well as the interconnecting white matter. In the conversion group, this generalized profile particularly involved working memory and verbal IQ and was positively correlated with limbic, insular and subcortical volumes as well as negatively related to prefrontal, temporal, parietal, and occipital cortices. Conversely, the neurocognitive profiles in the HC group were confined to working memory, learning and IQ, which were diffusely associated with cortical and subcortical brain regions. *Conclusions*: These findings suggest that the ARMS and prodromal phase of psychosis are characterized by a convergent mapping from multi-domain neurocognitive measures to a set of prefronto-temporo-limbic and subcortical structures. Furthermore, a neuroanatomical separation between positive and negative brain–cognition correlations may not only point to a biological process determining the clinical risk for disease transition, but also to possible compensatory or dysmaturational neural processes. *Hum Brain Mapp 00:000–000, 2011.*

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INTRODUCTION

From a very early stage, schizophrenia entails deficits in the executive, mnemonic, and perceptual domains of neurocognitive functioning [Frommann et al., 2010; Heinrichs and Zakzanis, 1998]. A direct link between these deficits and an underlying brain pathology has long been posited based on the concurrent evidence of neurocognitive and neuroanatomical abnormalities. This hypothesis was first supported by magnetic resonance imaging (MRI) studies [see Antonova et al., 2004; Crespo-Facorro et al., 2007a, for review] that mainly detected altered relationships between neuroanatomical and neuropsychological measures, e.g., attenuated correlations between prefrontal volumes and processing speed as well as reversed correlations between verbal memory performance and hippocampal volume in schizophrenic patients vs. healthy controls [Sanfilipo et al., 2002]. In summary, these investigations pointed to a distributed neural circuitry subserving disease-specific brain–cognition associations.

Abbreviations

ARMS	at-risk mental state for psychosis
ARMS-E/-L	"Early" ARMS/"Late" ARMS
ARMS-NT/-T	non-transitions/transitions to psychosis
DS	digit span test
DSM-IV	diagnostic and statistical manual of mental disorders, 4th edition
DST	digit-symbol test
GM(V)	gray matter (volume)
HC	healthy controls
ICD-10	international classification of diseases, 10th edition
LNS	letter-number span test
LV(s)	latent variable(s)
MADRS	Montgomery-Åsberg depression rating scale
MPRAGE	magnetization prepared rapid acquisition gradient echo
MRI	magnetic resonance imaging
MWT-B	Mehrfach-Wortschatz test B
PANSS	positive and negative symptom scale
PLS	partial least squares
RAVLT-IR	rey auditory verbal learning test—immediate recall
RAVLT-DR	rey auditory verbal learning test—delayed recall
TMT-A	trail-making test, part A
TMT-B	trail-making test, part B
SOPT	self-ordered pointing task
SPM	statistical parametric mapping
VBM	voxel-based morphometry
WM(V)	white matter (volume)

Overlapping but milder cognitive abnormalities have also been found in subjects at genetic risk for schizophrenia, such as the patients' offspring and unaffected relatives [Erlenmeyer-Kimling et al., 2000; Faraone et al., 1999; Hans et al., 1999; Owens and Johnstone, 2006]. Recently, these data have been complemented by clinical high-risk studies following either the Melbourne "ultra-high risk" approach [Yung et al., 1998] or a combination of predictive basic symptoms [Klosterkötter et al., 2001] and ultra-high risk criteria [Frommann et al., 2010; Pukrop et al., 2006; Simon et al., 2006]. These studies showed that clinically defined at-risk mental states for psychosis (ARMS) are associated with deficits in processing speed [Brewer et al., 2005; Niendam et al., 2006; Simon et al., 2007], sustained attention [Francey et al., 2005], verbal learning/memory [Lencz et al., 2006; Niendam et al., 2006; Pukrop et al., 2006; Simon et al., 2007] and executive functions [Hawkins et al., 2004; Pukrop et al., 2006; Simon et al., 2007]. Furthermore, recent voxel-based morphometry (VBM) studies revealed distributed brain abnormalities in the ARMS, which predominantly covered prefrontal, opercular, limbic, and paralimbic structures [Borgwardt et al., 2007; Job et al., 2003, 2005; Koutsouleris et al., 2009a,b; Meisenzahl et al., 2008b; Pantelis et al., 2003] similar to the established disease [Honea et al., 2005; Koutsouleris et al., 2008; Meisenzahl et al., 2008a]. These cross-sectional neurocognitive and neuroanatomical alterations may particularly relate to an ultra-high risk state for the disease as defined by the presence of subclinical psychotic symptoms [Borgwardt et al., 2007; Frommann et al., 2010; Koutsouleris et al., 2009b; Pukrop et al., 2007]. Moreover, longitudinal neuropsychological and morphometric studies revealed independently from each other (1) a deterioration of cognitive abilities, i.e., executive functioning [Wood et al., 2007], as well as a (2) progressive reduction of prefrontal, temporal, and cerebellar volumes in subsequent converters to psychosis [Borgwardt et al., 2008; Job et al., 2005; Koutsouleris et al., 2010a; Pantelis et al., 2003; Sun et al., 2009]. Taken together, these concurrent structural and neuropsychological findings point to an active biological process affecting both the neuroanatomical and neurocognitive dimensions as the disease unfolds during the transition from adolescence to adulthood [Pantelis et al., 2005].

In keeping with this hypothesis, Hurlemann et al. [2008] were the first to observe a direct link between reduced hippocampal volumes and verbal learning deficits in clinical ARMS subjects, which was most pronounced in the ultra-high risk state. Furthermore, our recent VBM analysis detected correlations between cognitive set-shifting impairments and prefronto-callosal regions, as

TABLE I. Inclusion/exclusion criteria

ARMS-E: ARMS subjects without APS and/or BLIPS . . .

(1) . . . 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)
- Derealization
- Visual perception disturbances
- Acoustic perception disturbances

and/or

(2) . . . showing a reduction in the Global Assessment of Functioning Score (DSM IV) 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

ARMS-L: ARMS subjects with/without basic symptoms, with/without global functioning and trait markers . . .

(1) . . . having at least one of the following Attenuated Psychotic Symptoms (APS) within the last three months, appearing several times per week for a period of at least 1 week:

- Ideas of reference
- Odd beliefs or magical thinking
- Unusual perceptual experiences
- Odd thinking and speech
- Suspiciousness or paranoid ideation

and/or

(2) . . . having at least one of the following Brief Limited Intermittent Psychotic Symptoms (BLIPS), defined as the appearance of one of the following psychotic symptoms for less than 1 week (interval between episodes at least 1 week), resolving spontaneously:

- Hallucinations
- Delusions
- Formal thought disorder
- Gross disorganized or catatonic behavior

Exclusion Criteria

- Disease transition as defined by Yung et al.
- 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
- Alcohol or drug abuse within three months prior to examination, following the DSM-IV criteria
- A past or present inflammatory, traumatic or epileptic diseases of the central nervous system
- Any previous treatment with antipsychotics prior to neurocognitive assessment
- Healthy controls: positive familial history of schizophrenic or affective psychoses in the first-degree relatives

well as a volumetric network linking these regions with further prefrontal, cerebellar and parietal areas [Koutsouleris et al., 2010b]. However, regarding the multifaceted behavioral and morphological alterations in the ARMS, these univariate approaches may have unveiled only a small fraction of the risk-specific associations between neuroanatomy and neurocognition. The greater portion of these associations may have been missed so far due the biological complexity of brain–behavior correlations, meaning that (1) a single brain structure may be involved across multiple cognitive functions, whereas (2) different sets of brain structures may contribute to a single cognitive process. This multiplicity of overlapping mappings constitutes a high-dimensional analytical problem [Davatzikos, 2004] that can only be adequately resolved using multivariate techniques, like Partial Least Squares (PLS), which are capable of revealing the hidden structure underlying the complexity of brain–cognition associations [Gilboa et al., 2005; Kawasaki et al., 2007; McIntosh and Lobaugh, 2004; Menzies et al., 2007; Nestor et al., 2002; Tura et al., 2008]. We used PLS to explore system-level covariance patterns between whole-brain structural imaging data and a comprehensive neuropsychological test battery obtained from a previously described population of clinical ARMS and

TABLE II. Neuropsychological test battery

Cognitive domain	Variables
Premorbid verbal IQ	
Mehrfach-Wortschatztest B (MWT-B)(Lehrl, 2005)	Raw score correct
Processing speed	
Trail-making test, part A (TMT-A)(Reitan, 1992)	Time to completion [s]
Digit symbol test (DST, [WAIS-III; Wechsler, 1997])	Raw score correct
Working memory	
Digit span test (DS, [WAIS-III; Wechsler, 1997])	Raw score correct
Letter number span test (LNS) [Gold et al., 1997]	Raw score correct
Subject-ordered pointing task (SOPT) [Petrides, 1995]	Error score
Verbal learning and memory	
Rey auditory verbal learning test (RAVLT) [Lezak, 1995]	Sum of raw score correct after trials 1–5 (RAVLT-IR) Raw score correct after delayed recall (RAVLT-DR)
Executive functions	
Trail-making test, part B (TMT-B) [Reitan, 1992]	Time to completion [s]
Verbal Fluency (letters) (VF) [Aschenbrenner et al., 2001]	Sum of correct responses

Cognitive domains were defined according to Schultze-Lutter et al. (2007b).

healthy control subjects [Koutsouleris et al., 2010b]. Based on the existing brain–cognition literature in schizophrenia [Antonova et al., 2004; Crespo-Facorro et al., 2007a], we expected that cross-domain neurocognitive performance in the ARMS would be linked to specific patterns of prefronto-temporo-limbic and subcortical regions not observed in healthy controls and (1) that physiological brain-cognition relationships found in healthy controls would be attenuated or absent in the ARMS. Furthermore, we hypothesized that these patterns would be particularly present in an ultra-high risk state compared to a milder ARMS, which is primarily defined by the presence of basic symptoms.

METHODS

Study Participants

Forty individuals in an ARMS for psychosis (Table III) and 30 healthy controls (HC) matched group-wise for age, gender, handedness, and premorbid verbal IQ were recruited at the Early Detection and Intervention Center for Mental Crises of the Clinic of Psychiatry and Psychotherapy, Ludwig-Maximilian-University, Germany, for MRI scanning and neuropsychological testing using an established operationalized recruitment protocol [Table I; Frommann et al., 2008, 2010; Koutsouleris et al., 2009a,b]. This protocol was based on a two-stage concept of the ARMS, distinguishing between an "early," or non-psychotic ARMS (ARMS-E), with an increased risk for psychosis, and a "late," or psychotic ARMS (ARMS-L), characterized by an imminent risk for disease transition. Exclusion criteria (Table I) were carefully assessed by evaluating the personal and familial history using a semi-structured clinical interview and the Structured Clinical Interview for DSM-IV [American Psychiatric Association, 1994]. In particular, candidate individuals with a present or past abuse of drugs (e.g., cannabis, opiates, and amphetamines) and/or alcohol (according to DSM-IV) were excluded from the study. Recruited ARMS individuals were rated using the Global Assessment of Functioning Scale of the DSM-IV, the Positive and Negative Symptom Scale (PANSS, Kay et al. [1987]) and the Montgomery-Åsberg Depression Rating Scale (MADRS, Montgomery and Åsberg [1979]).

ARMS subjects were regularly followed over 4 years to detect possible disease transitions. Subjects meeting the transition criteria of Yung et al. [1998] were diagnosed with a schizophrenia spectrum disorder using the ICD-10 research criteria at transition and after one year. Follow-up information could be obtained from 27 subjects after an average interval of 3.7 (SD: 1.1) years, consisting of 11 converters (ARMS-T: $n = 8$, schizophrenia, 3, schizoaffective psychosis), and 16 non-converters (ARMS-NT: $n = 14$ no psychiatric diagnosis, 2 major depression). Ten converters had been initially assigned to the ARMS-L and 1 to the ARMS-E subgroup. Out of the 13 subjects without follow-up, 6 could not be contacted or refused to participate, whereas 7 had not completed the follow-up. No antipsychotics were prescribed prior to MRI scanning and neuropsychological testing. All subjects provided their written informed consent before study inclusion. The study was approved by the Local Research Ethics Committee of the Ludwig-Maximilian-University.

Neuropsychological Testing

At the time of MRI scanning, nine standardized neuropsychological tests (Table II) were administered to all subjects by trained master-level neurophysiologists (K.K., J.S.,

P.D.) to assess cross-domain cognitive functioning, including premorbid verbal IQ, processing speed, working memory, verbal and visual memory, as well as executive functions [Schultze-Lutter et al., 2007b]. From these data, 10 test variables were computed (Table II) and adjusted for the effects of age and gender using partial correlations. The adjusted scores were z-transformed based on the respective HC data and entered analyses of variance that assessed between-group differences in (1) HC vs. ARMS, (2) HC vs. ARMS-E vs. ARMS-L, and (3) HC vs. ARMS-NT vs. ARMS-T. Significant between-group effects were examined for pairwise group differences using post-hoc Bonferroni tests. Adjustment for multiple comparisons was performed using Holm's sequential method [Holm, 1979]. Significance was defined at $P < 0.05$.

MRI Data Acquisition and Preprocessing

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 × 0.45 × 1.5 mm^3). All images were first carefully checked for MRI scanner artifacts and gross anatomical abnormalities by trained clinical neuroradiologists and then processed using the VBM8 toolbox [Gaser, 2008] and Statistical Parametric Mapping (SPM8, Wellcome Trust Centre for Neuroimaging [2009]) by following exactly the protocol described in Koutsouleris et al. [2010b]. In summary, the toolbox extends the unified segmentation model of SPM8 [Ashburner and Friston, 2005] by the (1) application of the Optimized Blockwise Nonlocal-Means Filter to increase the signal-to-noise ratio of the data [Coupé et al., 2006], (2) segmentation into gray matter (GM), white matter (WM) and cerebrospinal fluid using an adaptive maximum a posteriori approach [Rajapakse et al., 1997] extended by a partial volume estimation model [Manjón et al., 2008], (3) postprocessing using a hidden Markow Random Field model [Bach-Cuadra et al., 2005], and (4) high-dimensional registration to MNI space using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra toolbox [Ashburner, 2009, 2007; Bergouignan et al., 2009; Klein et al., 2009]. The normalized GM and WM maps were modulated to compare GM and WM volumes (GMV/WMV) across groups and smoothed with a 5-mm Gaussian kernel. The considerably improved anatomical overlap of individual tissue maps obtained using the high-dimensional normalization procedure allowed the use of a small kernel width, and thus facilitated a high spatial resolution of the multivariate statistical analysis.

Multivariate Statistical Analysis

We investigated system-level covariance patterns between neuroanatomy and neurocognition using PLS [Fujiwara et al., 2008; Giessing et al., 2007; Krishnan et al., 2010; Menzies et al., 2007] as implemented in the PLSgui toolbox (http://www.rotman-baycrest.on.ca). PLS is a multivariate, data-driven method that is well suited to capture multicollinear interactions between brain and behavior because it reduces high-dimensional brain–behavior correlations into a small set of latent variables (LVs) [Krishnan et al., 2010]. Each LV describes a distinct brain–behavior correlation pattern, which consists (1) of a singular image of volumetric effects covarying with the behavioral variables, and (2) of a profile of covariances between the behavioral measures and the singular image. Both these behavioral and the volumetric covariances, which describe the LV, are referred to as saliences. Furthermore, the expression of the singular image in each participant's brain is characterized by a global brainscore, the summed product of the singular image with the participant's GMV/WMV map. The set of LVs is sorted according to the singular values d_{LV}, which express the strength of association between volumetric and behavioral saliences in each LV.

A random effects model based on a non-parametric permutation test decides which of the LVs represent generalizable covariance patterns [Krishnan et al., 2010]. Each LVs' significance is determined at the whole-brain level by randomly reassigning the observations to the experimental predictors and recomputing the d_{LV} of the permuted PLS models. We performed 5,000 permutations to estimate the permutation distribution of d_{LV} and rejected the null hypothesis that the observed d_{LV} were obtained by chance at $\alpha = 0.05$. Furthermore, the stability of covariance elements was assessed by estimating the standard errors of the saliences on the LVs using 1,000 bootstrap resamplings [Efron and Tibshirani, 1986; Krishnan et al., 2010; McIntosh and Lobaugh, 2004]. Voxels with an absolute ratio of salience to standard error ≥ 2, corresponding to 95% confidence limits, were considered reliable as they showed little variation of their experimental effects [Krishnan et al., 2010; McIntosh and Lobaugh, 2004; Sampson et al., 1989]. Reliable pattern elements of significant LVs were mapped to anatomical regions using Automated Anatomical Labeling [Tzourio-Mazoyer et al., 2002] (see Supporting Information).

The following strategy was employed to investigate brain–cognition covariance patterns across groups (see Fig. 1). Initially, an omnibus test of between-group effects assessed multivariate neurocognition x tissue type (smoothed GMV/WMV maps) x group (HC/ARMS) interactions. Therefore, we created a behavioral design matrix by (1) group-wise sorting the 10 z-transformed, unadjusted neurocognitive predictors, as well as age and gender and (2) replicating each group's predictor matrix across the GMV/WMV tissue conditions. Then, we computed the covariance between this design matrix and the smoothed tissue maps stacked across the HC and ARMS groups. This covariance matrix was decomposed into a series of LVs by means of singular value decomposition [Krishnan et al.,

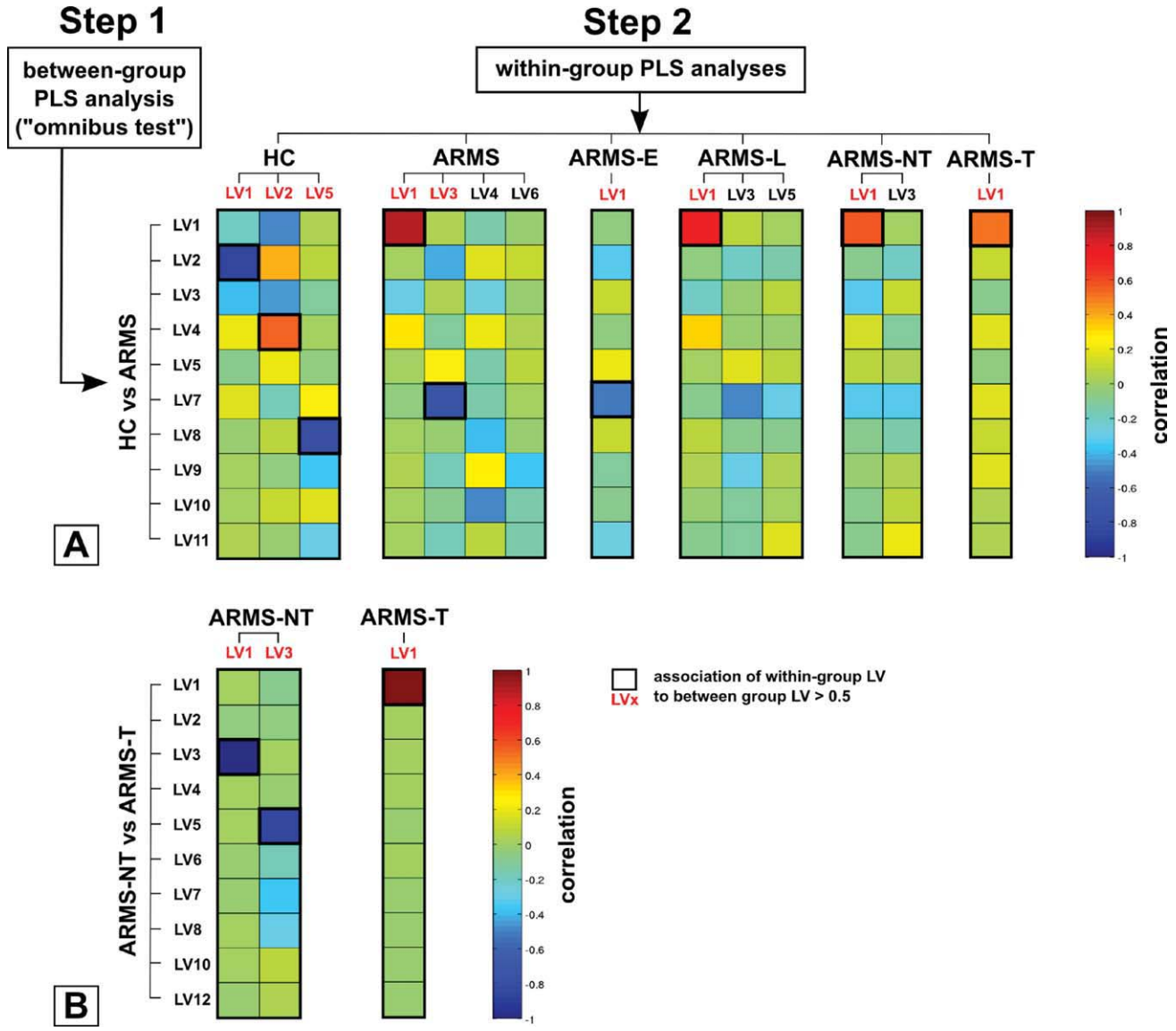


Figure 1.

Inner product analyses of between-group LVs to within-group LVs. The correlation matrices represent the pairwise inner products computed between the singular images of significant between-group LVs (**A:** Behavioral PLS analysis of HC vs. ARMS; **B:** Behavioral PLS analysis of ARMS-NT vs. ARMS-T) and the singular images of significant within-group LVs (A: Behavioral PLS analyses of HC, ARMS, ARMS-E, ARMS-L, ARMS-NT, and ARMS-T; B: Behavioral PLS analyses of ARMS-NT and ARMS-T). Absolute correlations coefficients $\geq$0.5 were highlighted as the respective within-group LVs were further detailed in the present study.

2010]. Permutation testing revealed that 10 of the 48 LVs in this between-group model (12 predictors $\times$ 2 tissue types $\times$ 2 groups) were significant (Table V). To evaluate whether our study groups were differentially or conjointly involved in these 10 brain–cognition patterns, we employed a post-hoc analysis, by first conducting two within-group PLS analyses for the HC and ARMS samples, respectively. Then, we assessed how strongly the within-group brain–cognition covariance patterns contributed to the between-group effects. Therefore, we evaluated the correlations of significant within-group to significant between-group LVs by computing the inner products of the respective singular images (see Fig. 1). This procedure resulted in a correlation matrix, from which within-group LVs explaining $\geq$25% of

the common variance (correlation $\geq$0.5) were further examined. This cutoff was chosen to focus the analysis on the most informative covariance patterns.

Additionally, we performed within-group PLS analyses for each of the ARMS-E, ARMS-L, ARMS-NT, and ARMS-T subgroups and computed the inner products between the significant LVs of these models and the significant between-group LVs of HC vs. ARMS. These analyses aimed at assessing whether the brain–cognition covariance patterns observed in HC vs. ARMS (1) were particularly expressed in an ultra-high risk for psychosis (ARMS-L vs. ARMS-E) and (2) were mainly driven by the transition vs. the non-transition group. Furthermore, brain–cognition covariance patterns specifically associated with illness transition were explored in a separate omnibus ARMS-NT vs. ARMS-T test and further examined using the post-hoc framework described above. Again, within-group LVs with a correlation $\geq$0.5 were further examined.

RESULTS

Sociodemographic, Clinical, and Global Anatomical Variables

No significant differences in the sociodemographic variables were detected in any group comparison, except for age in the ARMS-T compared to the other groups (Table III). Furthermore, the genetic risk for schizophrenic or affective psychoses did not differ between the ARMS subgroups. More pronounced psychopathological abnormalities were observed in ARMS-L vs. ARMS-E regarding the PANSS positive score and in ARMS-T vs. ARMS-NT regarding the PANSS total, positive and negative score. ARMS-NT scored higher in the MADRS compared to ARMS-T.

Neurocognitive Test Battery

Significant between-group differences were identified primarily in the processing speed, executive functioning, visual working memory and verbal learning domains (Table IV). The ARMS group performed worse in the TMT-B and SOPT vs. HC. Further neurocognitive deficits involving the DST, TMT-A, TMT-B, SOPT, RAVLT-IR, and RAVLT-DR were identified in the HC vs. ARMS-E vs. ARMS-L subgroup analysis, which were mainly driven by ARMS-L who scored significantly below HC and ARMS-E across these tests, with the exception of the SOPT, which was almost equally reduced in ARMS-E and ARMS-L. Similar neurocognitive deficits were observed in HC vs. ARMS-NT vs. ARMS-T, consisting of (1) significant TMT-B, SOPT, RAVLT-IR and RAVLT-DR deficits in ARMS-T vs. HC, (2) TMT-B, SOPT and RAVLT-IR impairments in ARMS-NT vs. HC, and (3) pronounced, but non-significantly reduced performances in ARMS-T vs. ARMS-NT, particularly in the TMT-B and RAVLT-DR.

Brain–Cognition PLS Analyses

HC vs. ARMS

Inner product analysis. Ten LVs were significant in the omnibus test, accounting for 56.3% of the covariance between brain structure, neurocognition, age, and gender (Table V, Fig. 1A). The permutation test of the within-group PLS models detected three significant LVs in the HC and four in the ARMS group. As shown in the inner product matrix of Figure 1A, a strong correlation existed between the singular images of between-group LV1 and the LV1 of the within-group ARMS model ($r_{LV1} = 0.90$), which was weaker or not present in the HC model ($r_{LV1} = -0.22$; $r_{LV2} = -0.48$; $r_{LV5} = 0.04$). This effect was driven by the ARMS-L group because the singular images of between-group LV1 and LV1 of ARMS-L were highly correlated ($r_{LV1} = 0.72$), while no such correlation was found in the ARMS-E model ($r_{LV1} = -0.06$). However, the between-group LV1 covariance pattern was not specifically associated with transition to psychosis as the LV1 of both the ARMS-NT and ARMS-T models were similarly correlated to between-group LV1 (ARMS-NT: $r_{LV1} = 0.58$; ARMS-T: $r_{LV1} = 0.52$).

A strong correlation ($r = -0.78$) existed between the singular images of between-group LV7 and the LV3 of the ARMS model. This correlation was not specifically driven by the ARMS-L ($r_{LV3} = -0.50$) or ARMS-E ($r_{LV1} = -0.53$) groups and was absent/weak in the significant LVs of the HC model ($r_{LV1} = 0.17$, $r_{LV2} = -0.16$, $r_{LV5} = -0.22$) or the ARMS-NT ($r_{LV1} = -0.33$, $r_{LV3} = -0.31$) and ARMS-T models ($r_{LV1} = -0.19$). In contrast, HC-specific correlations were found between the singular images of between-group LV2, LV4, and LV8 and within-group LV1 ($r = -0.85$), LV2 ($r = 0.54$) and LV5 ($r = -0.80$), respectively. These between-group LVs were not correlated to the LVs of the ARMS model or the ARMS subgroup analyses.

Within-group HC analysis. The profile of LV1 ($P = 0.012$, 13.7% covariance; Table V, Fig. 2A, and Supporting Information Table I) consisted of reliable positive correlations between the HC individuals' GM/WM brainscores and premorbid verbal IQ, (visual) working memory and verbal learning as well as age. This profile was present in the positive GM saliences, located predominantly in (1) the temporal pole, inferior temporal and fusiform gyrus, with extensions to the olfactory and parahippocampal gyri as well as the inferior occipital cortex, (2) the right superior parietal GMV, and (3) the thalamus, cerebellum and vermis. Furthermore, positive brain–age and brain–cognition correlations were also present in the positive WM saliences, which mapped mainly to the fornix, the right corticospinal tract and the middle cerebellar peduncle. In GM/WM structures showing negative saliences (occipital, parietal cortices, corpus callosum) the

TABLE III. Analysis of sociodemographic, clinical, and global anatomical variables

	HC	ARMS	T/χ^2	*P*	ARMS-E	ARMS-L	F/χ^2	*P*	ARMS-NT	ARMS-T	F/χ^2	*P*
Sociodemographic variables												
N	30	40			17	23			16	11		
Age: mean (SD) [years]	26.0 (2.7)	24.5 (5.9)	1.51	n.s.	25.5 (5.6)	23.7 (5.9)	1.57	n.s.	26.0 (6.8)	21.6 (3.3)	4.64	<0.05
Gender: male/female (%)	18/12 (60/40)	27/13 (67.5/32.5)	1.27	n.s.	10/7 (58.8/41.2)	17/6 (73.9/26.1)	1.39	n.s.	11/5 (68.8/31.3)	9/2 (81.8/18.2)	0.58	n.s.
Handedness: right/left/ ambidextruous (%)	29/1/0 (96.7/3.3/0)	33/4/3 (82.5/10.0/7.5)	0.42	n.s.	14/2/1 (82.4/11.8/5.9)	19/2/2 (82.6/8.7/8.7)	4.02	n.s.	12/3/1 (75.0/18.8/6.3)	11/0/0 (100/0/0)	3.23	n.s.
School education: mean (SD) [years]	12.4 (1.2)	11.9 (1.2)	2.51	n.s.	12.2	11.6	1.99	n.s.	11.8 (1.3)	11.6 (1.2)	1.28	n.s.
Verbal IQ (MWT-B): mean (SD)	109.7 (8.3)	107.0 (14.4)	1.00	n.s.	110.1 (13.8)	104.7 (14.7)	1.41	n.s.	111.3 (14.1)	104.2 (17.3)	1.19	n.s.
No. (%) of first-degree relatives with schizophrenic psychoses	—	6 (15.0)	—	—	2 (11.8)	4 (17.4)	0.24	n.s.	3 (18.8)	2 (18.2)	0.001	n.s.
No. (%) of first-degree relatives with affective psychoses	—	7 (17.5)	—	—	5 (29.4)	2 (8.7)	2.91	n.s	4 (25.0)	2 (18.2)	0.18	n.s.
Clinical variables: mean (SD)							***F***	***P***			***F***	***P***
GAF score	—	58.6 (11.6)	—	—	61.0 (8.8)	56.8 (13.5)	0.49	n.s.	59.1 (11.9)	60.0 (15.4)	0.16	n.s.
PANSS total score	—	60.1 (18.6)	—	—	56.8 (14.0)	64.7 (22.5)	1.64	n.s.	48.2 (9.1)	65.3 (21.3)	5.48	<0.05
PANSS positive score	—	12.2 (4.2)	—	—	9.9 (2.6)	14.6 (4.5)	13.4	<0.001	9.6 (2.2)	14.5 (3.8)	9.16	<0.01
PANSS negative score	—	15.7 (7.9)	—	—	14.9 (6.7)	16.8 (8.8)	0.34	n.s.	11.2 (4.3)	18.5 (9.4)	5.53	<0.05
PANSS general score	—	32.2 (9.4)	—	—	32.0 (7.9)	33.3 (11.2)	0.42	n.s.	27.5 (5.5)	32.3 (11.2)	1.70	n.s.
MADRS score	—	15.2 (8.9)	—	—	18.6 (8.3)	12.5 (8.6)	1.25	n.s	16.0 (4.8)	6.4 (3.5)	12.59	<0.01
Global Anatomical Parameters [ml]: mean (SD)			***F***	***P***			***F***	***P***			***F***	***P***
Gray matter volume	610.5 (36.9)	635.1 (63.3)	1.67	n.s.	623.9 (52.5)	643.4 (70.2)	0.78	n.s.	619.3 (58.7)	676.1 (57.7)	2.72	n.s.
White matter volume	613 (63.4)	621.8 (70.3)	0.52	n.s.	627.6 (75.6)	617.5 (67.4)	0.49	n.s.	625.0 (83.0)	629.6 (54.9)	0.45	n.s.
Cerebrospinal fluid volume	199.8 (22.9)	199.5 (28.1)	0.05	n.s.	206.1 (27.0)	194.6 (28.5)	1.11	n.s.	199.0 (34.2)	200.5 (22.0)	0.04	n.s
Total intracranial volume	1423.9 (106.7)	1456.4 (126.8)	0.74	n.s.	1457.6 (128.2)	1455.5 (128.6)	0.69	n.s.	1443.0 (144.2)	1506.0 (102.1)	0.99	n.s.

Abbreviations: *ARMS* At-Risk Mental State for psychosis, *ARMS-E* early ARMS subgroup, *ARMS-L* late ARMS subgroup, *ARMS-NT* non-conversion subgroup, *ARMS-T* conversion subgroup, *GAF* Global Assessment of Functioning, *HC* Healthy Control subjects, *PANSS* Positive and Negative Symptom Scale, *F* main effect's F value, *T* Student's *t* test value, χ^2 Pearson χ^2 value. Schooling years, clinical and global anatomical variables were assessed using ANCOVA designs, with group entered as main effect and age and gender defined as covariates of no interest. All *P* values are two-sided and exact in case of nonparametric tests.

TABLE IV. Statistical analysis of between-group differences in the 10 neurocognitive test measures

	HC vs. ARMS: *t* test			HC vs. ARMS-E vs. ARMS-L: ANOVA and Post-hoc analyses							HC vs. ARMS-NT vs. ARMS-T: ANOVA and Post-hoc analyses						
	ARMS: mean (SD)	*T*	*P*	ARMS-E: mean (SD)	ARMS-L: mean (SD)	*F*	*P*	HC vs. ARMS-E	HC vs. ARMS-L	ARMS-E vs. ARMS-L	ARMS-NT: mean (SD)	ARMS-T: mean (SD)	*F*	*P*	HC vs. ARMS-NT	HC vs. ARMS-T	ARMS-NT vs ARMS-T
MWT-B	−0.33 (1.73)	1.00	0.323	0.04 (1.66)	−0.61 (1.76)	1.41	0.252				0.18 (1.69)	−0.67 (2.07)	1.19	0.311			
DST	−0.66 (1.13)	0.69	0.495	−0.08 (1.03)	−1.1 (1.01)	8.65	0.000*	1.000	0.001*	0.007*	−0.67 (1.25)	−1.03 (0.7)	4.87	0.011			
DS	−0.18 (1.13)	0.34	0.734	0.11 (1.17)	−0.39 (1.08)	1.32	0.273				0.28 (0.89)	−0.54 (1.26)	2.11	0.131			
LNS	−0.8 (2.9)	0.03	0.974	−0.12 (2.57)	−1.3 (3.08)	2.41	0.098				−0.37 (3.61)	−0.92 (2.02)	0.71	0.494			
TMT-A	−0.58 (1.48)	2.30	0.025	0.04 (1.1)	−1.04 (1.58)	5.55	0.006*	1.000	0.011*	0.025*	−0.27 (1.65)	−0.77 (1.35)	1.47	0.239			
TMT-B	−1.56 (1.83)	4.25	0.000*	−0.78 (1.48)	−2.13 (1.88)	13.95	0.000*	0.241	0.000*	0.016*	−1.54 (2.04)	−2.56 (1.3)	15.26	0.000*	0.003*	0.000*	0.213
SOPT	−2.13 (2.26)	5.69	0.000*	−2.1 (2.73)	−2.15 (1.91)	11.34	0.000*	0.001*	0.000*	1.000	−2.53 (2.58)	−2.6 (1.96)	14.99	0.000*	0.000*	0.000*	1.000
RAVLT-IR	−1.43 (1.63)	1.44	0.153	−0.75 (1.29)	−1.94 (1.69)	13.86	0.000*	0.200	0.000*	0.021*	−1.24 (1.67)	−1.71 (1.72)	8.21	0.001*	0.014*	0.002*	1.000
RAVLT-DR	−1.77 (2.38)	2.10	0.040	−0.93 (1.62)	−2.39 (2.69)	10.88	0.000*	0.305	0.000*	0.049*	−1.34 (2.6)	−2.57 (2.61)	7.90	0.001*	0.084	0.001*	0.320
VF	−0.19 (1.44)	0.61	0.541	0.21 (1.54)	−0.47 (1.33)	1.62	0.205				0.003 (1.23)	−0.57 (1.64)	1.01	0.371			

Neurocognitive test scores were adjusted for the effects of age and gender and standardized according to respective means and standard deviations of the HC data. For each neurocognitive test variable, statistical comparisons were conducted to evaluate group-level differences between HC vs. ARMS (*t* test) as well as HC vs. ARMS-E vs. ARMS-L and HC vs. ARMS-NT vs. ARMS-T (ANOVA). The Holm-Bonferroni correction was employed to correct the *P* values for multiple comparisons and significant between-group differences were flagged with an asterisk. In these cases, a Bonferroni post-hoc analysis was carried out to determine the significance of pairwise group differences. Abbreviations of neuropsychological test variables are detailed in Table 2 and in the Abbreviations list.

brain–age and brain–cognition correlations described above were reversed.

The profile of LV2 ($P = 0.001$, 12.7% covariance) involved positive correlations between GM/WM brainscores and age, sex and premorbid verbal IQ (Table V, Fig. 2B, and Supporting Information Table I). Positive correlations were also found between GM brainscores and processing speed, while negative correlations were detected between WM brainscores and working memory. This correlation profile mapped to positive GM saliences mainly located in (1) the medial, lateral and orbital prefrontal cortices with extensions to the cingulate and supplementary motor cortices, bilaterally, (2) the opercular region (ventromedial prefrontal cortex, insula, angular gyrus), (3) the lateral parietal regions, and (4) in the medial portions of the cerebellar hemispheres and the vermis. Moreover, this correlation profile was present in positive WM saliences mainly observed in the left sagittal stratum, the inferior fronto-occipital fascicle and the external capsule. The correlation profile was reversed in voxels with negative GM saliences, involving the (1) premotor and motor cortices, bilaterally, (2) opercular structures (ventromedial, insular and superior temporal cortices), (3) inferior temporal and fusiform regions with extensions to the medial occipital cortex, and (4) cerebellum and vermis. Negative WM saliences were observed in the corona radiata, the fornix, and the cerebellar WMV.

The neurocognitive profile of LV5 ($P = 0.040$, 7.0% covariance) consisted of positive GM/WM brainscore correlations with immediate verbal learning and negative correlations with verbal fluency. Differential effects within the GM condition involved positive/negative correlations with processing speed/working memory. No reliable age and gender covariation was detected (Table V, Fig. 2C). This correlation profile mapped to positive GM saliences in the lateral prefrontal, the left supramarginal and the bilateral occipital cortices as well as to positive WM saliences in the left anterior corona radiata. It was reversed in negative GM saliences found in the limbic and perisylvian structures and negative WM saliences observed in the corona radiata, cingulum/fornix, sagittal stratum, and internal capsule.

Within-group ARMS analysis. The profile of LV1 (Table V: $P < 0.001$, 18.8% covariance) consisted of positive correlations between all neurocognitive measures (except for the SOPT) and the GM/WM brainscores (Table V, Fig. 3, and Supporting Information Table I). Within this pattern, the strongest correlations were observed in the executive functions and verbal learning domains, while working memory and premorbid verbal IQ showed the weakest associations. Furthermore, we identified reliable brainscore correlations for age and gender. This correlation profile mapped to positive GM saliences within (1) the ventromedial prefrontal and orbitofrontal cortices, (2) the inferior frontal gyrus, left insula and supramarginal gyrus, (3) the hippocampus, parahippocampus and posterior cingulate cortex, (4) the caudate nuclei and right thalamus, and (5) the right occipital cortex. Positive WM saliences were left-pronounced and involved the corona radiata, corpus callosum, fornix and cingulum, uncinate fascicle, superior fronto-occipital fascicle, and the internal capsule. The profile of brain–cognition, brain–age, and brain–sex correlations was reversed in the negative GM saliences, including (1) portions of the lateral and inferior temporal cortices, bilaterally, (2) the Rolandic

TABLE V. Random effects analysis of between-group and within-group PLS models

	LV#	*P*	Covariance (%)
HC vs ARMS	1	<0.001	9.1
	2	<0.001	7.9
	3	0.014	7.0
	4	0.031	6.9
	5	0.001	6.1
	7	<0.001	4.9
	8	<0.001	4.1
	9	0.001	3.7
	10	0.015	3.4
	11	<0.001	3.2
			Sum: 56.3
HC	1	0.012	13.7
	2	0.001	12.7
	5	0.040	7.0
			Sum: 33.4
ARMS	1	<0.001	18.8
	3	<0.001	11.1
	4	0.001	8.8
	6	0.005	5.6
			Sum: 44.3
ARMS-E	1	<0.001	18.2
ARMS-L	1	0.015	30.0
	3	<0.001	9.8
	5	0.05	6.0
			Sum: 35.8
ARMS-NT vs ARMS-T	1	<0.001	19.6
	2	0.021	13.6
	3	<0.001	9.8
	4	0.047	7.7
	5	<0.001	5.0
	6	0.004	4.2
	7	0.002	4.0
	8	0.05	3.0
	10	0.018	2.9
	12	0.016	2.5
			Sum: 72.3
ARMS-NT	1	<0.001	22.8
	3	0.020	10.5
			Sum: 33.3
ARMS-T	1	0.028	33.2

Abbreviations: *LV* # No. of the significant ($P < 0.05$) latent variable, *P* significance as determined by non-parameteric permutation testing, Covariance (%) percentage of the total brain–behavior covariance explained by the respective latent variable.

opercula, left angular gyrus, right supramarginal gyrus, and (3) the medial and superior occipital cortices. Negative WM saliences were detected in the left tapetum.

Similar to LV1, the profile of LV3 ($P < 0.001$, 11.1% covariance) was characterized by (1) an opposite effect between age and neurocognitive correlations in both tissue conditions and (2) a neurocognitive involvement restricted to processing speed, (visual) working memory and verbal learning. This correlation profile was mainly associated with left-lateralized positive GM saliences, covering (1) the prefrontal and cingulate cortices, (2) the lateral and inferior temporal regions, (3) the olfactory and parahippocampal cortices, and (4) the cerebellum. Positive WM saliences were confined to the anterior corona radiata, corpus callosum, right sagittal stratum, and cerebellar peduncles. The correlation profile of LV3 was reversed in the negative GM saliences found in the (1) left perisylvian region, (2) thalamus, basal ganglia and mesencephalic structures, (3) occipital cortex, and (4) cerebellum. Negative WM saliences involved the right superior and inferior fronto-occipital fascicle, right internal capsule, and brainstem.

ARMS-NT vs. ARMS-T

Inner product analysis. Ten LVs were significant in the omnibus test, explaining 72.3% covariance. The permutation analysis of the ARMS-NT and ARMS-T models detected two significant LVs in the former and one in the latter group (Table V, Fig. 1B). A pronounced correlation between the singular images of between-group LV1 and LV1 of the ARMS-T model ($r = 0.99$) was detected in the inner product analysis (Fig. 1B), which was not present in the significant LVs of the ARMS-NT model ($r_{LV1} = 0.02$; $r_{LV3} = 0.09$). Conversely, specific correlations between the singular images of the omnibus test and the ARMS-NT model were found for between-group LV3/LV5 and within-group LV1 ($r = -0.99$)/LV3 ($r = -0.85$), respectively.

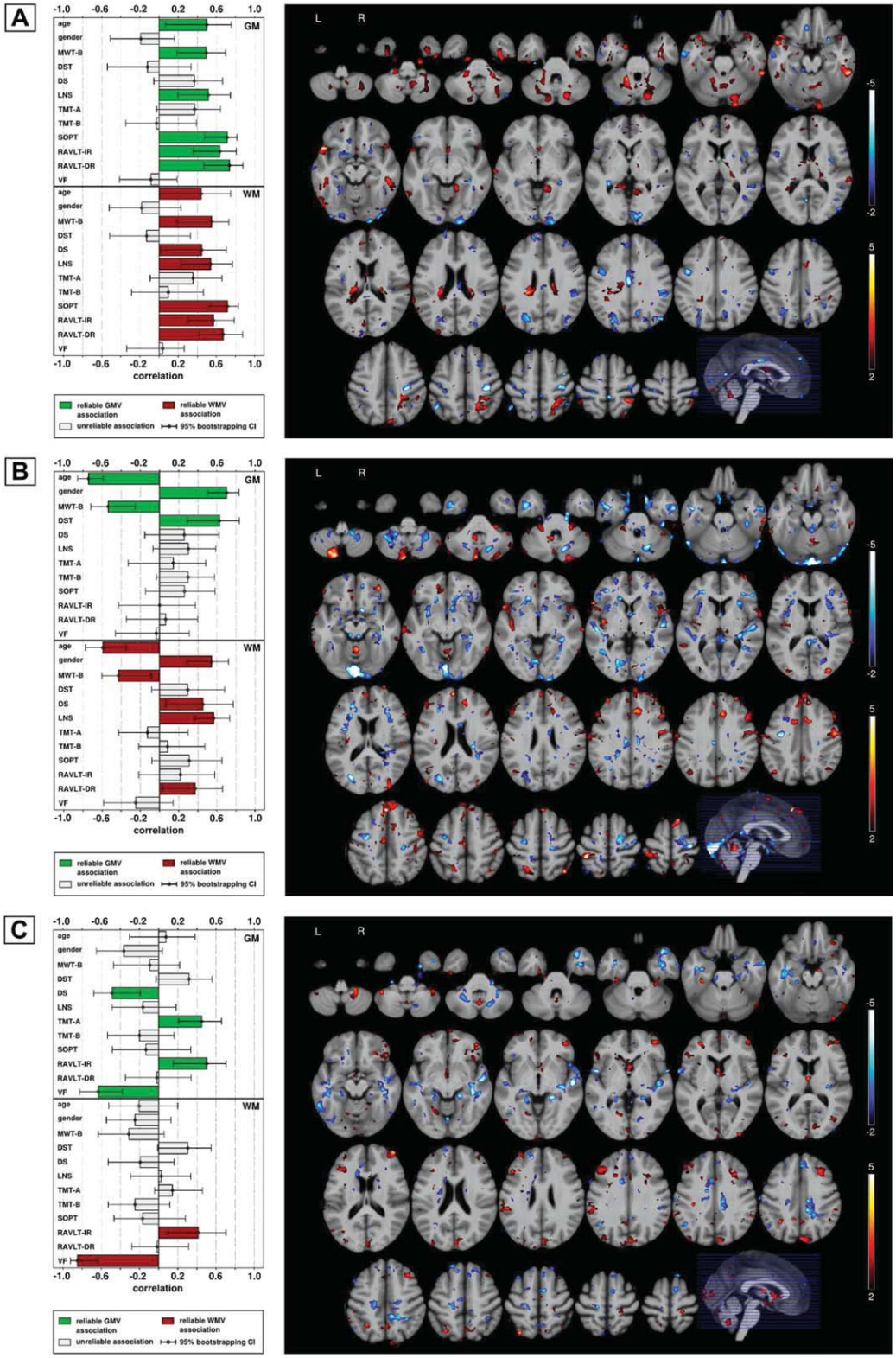
Within-group ARMS-NT analysis. The profile of LV1 ($P < 0.001$, 22.8% covariance) involved positive correlations between GM/WM brainscores and processing speed, executive functioning, verbal learning, and age (Table V, Fig. 4, and Supporting Information Table I). This correlation profile mapped to positive GM saliences, located within the (1) prefrontal, anterior cingulate and olfactory regions, (2) caudate nucleus, and (3) cerebellum. Positive WM saliences were identified in the anterior corona radiata, bilaterally, with left-lateralized extensions to the corpus callosum, fornix and uncinate fascicle, as well as in the left superior longitudinal and fronto-occipital fascicle, internal capsules, and right corticospinal tract. The brain–cognition and brain–age correlations were reversed in negative GM saliences covering portions of the dorsomedial prefrontal, middle and inferior temporal and occipital cortices as well as the putamen. Further left-lateralized negative GM saliences were detected in the thalamus and the perisylvian region, while right-lateralized saliences were detected in the parietal areas. Negative WM saliences were observed in the left external capsule, as well as in the right cingulum, inferior fronto-occipital fasciculus, intenal and external capsules, as well as the cerebellar and pontine WMV.

LV3 was significant at $P = 0.020$, accounting for 10.5% of the covariance (Table V). Similar to LV1, we observed positive correlations between GM/WM brainscores and age, premorbid verbal IQ and working memory, whereas negative correlations for gender, visual working memory, and verbal learning measures (Fig. 4A). This correlation profile involved positive GM saliences within the prefrontal and middle temporal cortices, as well as the supplementary motor/premotor areas, perisylvian regions, posterior cingulate cortex, and the cerebellum. Positive WM saliences were confined to the left uncinate fascicle and internal capsule, as well as to the right cerebral peduncle. The correlation profile of LV3 was reversed in negative GM saliences located mainly in the left fusiform and angular gyrus, as well as the right dorsomedial prefrontal and cingulate cortex and the pallidum. We identified negative WM saliences within the (1) corona radiata, (2) bilateral cingulum, (3) right superior longitudinal fascicle and left sagittal stratum, (4) left internal and right external capsule, and (5) the left thalamic radiation.

Within-group ARMS-T analysis. The profile of LV1 ($P = 0.028$, 33.2% covariance) consisted of positive brainscores correlations across all predictors in both tissue conditions (Table V, Fig. 5, and Supporting Information Table I). The highest correlations were observed in the (visual) working memory domain, the lowest in the verbal learning domain. This correlation profile mainly involved positive GM saliences in the basal ganglia, medial temporal lobe structures, insular cortices and left STG. Positive WM saliences were detected in the uncinate fascicle, fornix and cingulum, internal and external capsules, superior and inferior fronto-occipital fascicles, right sagittal stratum, superior and posterior corona radiata and the brainstem WMV. Brainscore correlations were reversed in negative GM saliences found in the (1) middle, inferior and fusiform cortices, (2) Rolandic opercula and supramarginal gyri, (3) prefrontal, orbitofrontal and olfactory cortices, and (4) the cerebellum. Negative WM saliences were confined to the right cingulum.

DISCUSSION

This study employed state-of-the-art analysis tools to reveal multivariate associations between neuroanatomy and neurocognition that specifically marked an elevated risk for developing psychosis. These findings were obtained in a neuroleptic-naïve ARMS population recruited using established operationalized high-risk criteria [Frommann et al., 2008, 2010; Hurlemann et al., 2008; Koutsouleris et al.,


A
B
C
-1.0 -0.6 -0.2 0.2 0.6 1.0
age
gender
MWT-B
DST
DS
LNS
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SOPT
RAVLT-IR
RAVLT-DR
VF
GM
WM
correlation
reliable GMV association
reliable WMV association
unreliable association
95% bootstrapping CI
L
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-5
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2

Figure 2.

2009a,b; Meisenzahl et al., 2008b; Quednow et al., 2008; Ruhrmann et al., 2003, 2010; Schultze-Lutter et al., 2007a]. The sociodemographic and clinical characteristics of our population are in line with previous investigations employing the combined basic symptoms-UHR approach to study neurocognitive and/or neuroanatomical abnormalities in the ARMS [Hurlemann et al., 2008; Pukrop et al., 2007, 2006; Schultze-Lutter et al., 2007b]. Moreover, the transition rate of 41% in the subgroup of 27 ARMS subjects with available clinical follow-up is in keeping with the literature, supporting that our sample is representative of an elevated vulnerability for psychosis [Cannon et al., 2008; Larsen, 2002; Miller et al., 2002; Yung et al., 2003].

Profiles of Neurocognitive Deficits in the ARMS for Psychosis

The entire ARMS group was impaired in the executive functioning and visual working memory domains, ranging on average 1.5–2.0 standard deviations below the performance of healthy controls. The considerable heterogeneity of neurocognitive data reported by previous ARMS studies regarding the type and degree of affected neuropsychological measures makes it difficult to exactly refer to the literature within the scope of this study [see Pukrop and Klosterkötter, 2010, for review]. Nonetheless, the profile of neurocognitive deficits observed in our ARMS subjects partly overlaps with previous findings of impaired neuropsychological test measures in (1) ARMS vs. normative data [Hawkins et al., 2004; Niendam et al., 2006; Schall et al., 2003] or (2) ARMS vs. HC [Lencz et al., 2006; Seidman et al., 2010]. A broader spectrum of neurocognitive deficits involving processing speed, verbal learning/memory, and executive functioning was associated with an ultra-high risk for psychosis as expressed by the ARMS-L group. Particularly, the latter two domains also differentiated the conversion from the non-conversion group, albeit not to a level reaching statistical significance. In contrast, the ARMS-E individuals were unimpaired in processing speed and showed only non-significant deficits in verbal memory/learning. These findings are consistent with recent cross-sectional and longitudinal studies reporting a deterioration and broadening of neuropsychological deficits across subsequent ARMS stages, meaning that these deficits are initially confined to circumscribed domains and subsequently intensify/generalize across multiple neurocognitive dimensions in parallel with the onset of overt psychosis [Frommann et al., 2010; Pukrop et al., 2006, 2007; Simon et al., 2007; Wood et al., 2007]. Conversely, the stability of pronounced visual working memory deficits across ARMS-E and ARMS-L, ARMS-NT, and ARMS-T may suggest that the SOPT marks an elevated vulnerability for psychosis that may not be linked to the ultimate illness transition. This observation, however, contrasts with previous ARMS investigations that reported SOPT deficits in ARMS-L vs. ARMS-E [Frommann et al., 2010; Pukrop et al., 2006] and ARMS-T vs. ARMS-NT individuals [Pukrop et al., 2007]. These inconsistencies may result from the prevailing cross-sectional design in the literature. Therefore, larger longitudinal studies are needed to clarify the trajectory of neuropsychological deficits in emerging psychosis.

Brain–Cognition Covariance Patterns in the ARMS

To the best of our knowledge, this is the first study to report on brain–cognition covariance patterns (1) extracted from whole-brain, structural MRI data and neuropsychological measures obtained across different cognitive domains and (2) related to a clinically defined risk for the development of schizophrenic psychosis. In summary, PLS revealed qualitatively different brain–cognition associations in HC vs. ARMS subjects consistent with our first hypothesis and previous MRI studies investigating the relationships between brain structure and neurocognition in *established* psychosis [see Antonova et al., 2004; Crespo-Facorro et al., 2007a, for review]. These studies demonstrated a disease-specific disruption/reversal of physiological brain–cognition relationships in schizophrenia. In this context, Sanfilipo et al. [2002] reported attenuated correlations between prefrontal volumes

Figure 2.

Latent variables 1, 2, and 5 of the within-group HC analysis. Left: For the LVs described in part **A** (LV1), **B** (LV2), and **C** (LV5) of the figure, the correlations between the GM (green)/WM (dark red) brainscores and the age, gender, and neurocognitive data of the HC subjects were depicted as bar graphs. Whiskers indicate the 95% confidence intervals of the correlation coefficients as determined by the PLS bootstrapping procedure. Correlations with zero-crossing confidence intervals were considered unreliable and hence were painted in light gray to facilitate the interpretation of the covariance patterns represented by each LV. Abbreviations of neuropsychological test variables are detailed in Table II. Right: The slice images of A, B, and C show the neuroanatomical mapping of reliable brain saliences with an absolute bootstrap ratio $\geq$2, corresponding to 95% confidence intervals. Using the software package MRIcron (C. Rohrden, http://www.sph.sc.edu/comd/rorden/mricron/), the positive (warm color scale) and negative (cool color scale) saliences were overlaid on the average normalized and skull-stripped T1-image computed from the data of all study participants. Brain regions with negative brain saliences express inversely the pattern of neurocognitive, age and gender loadings described on the left side of the figure.

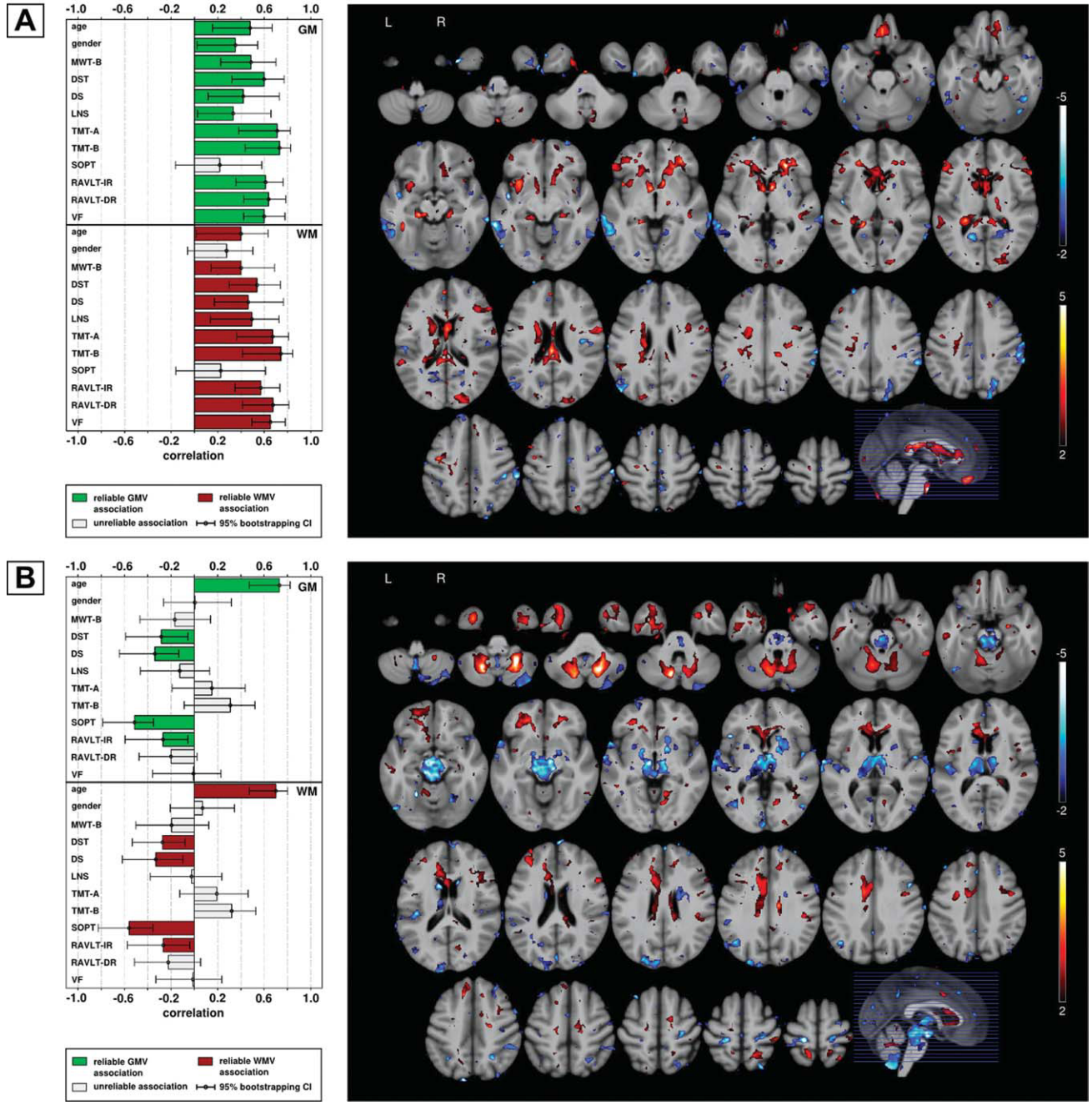

Figure 3.

Latent variables 1 and 3 of the within-group ARMS analysis. See the legend of Figure 2 for a description of the left and right parts of the figure and Table II for the abbreviations of neuropsychological tests.

and processing speed as well as reversed correlations between hippocampal volume and verbal memory in schizophrenic patients (SZ) vs. HC. Moreover, Salgado-Pineda et al. [2003] detected correlations between sustained attention and GM density in frontal, thalamic, and temporo-parietal regions of SZ, but not HC subjects. Finally, Antonova et al. [2005] found a positive association between precuneus volume and verbal memory in SZ, whereas a positive association between inferior frontal volumes and mnemonic functions in HC.

In keeping with our previous univariate analysis of neuroanatomical correlates of executive dysfunction in

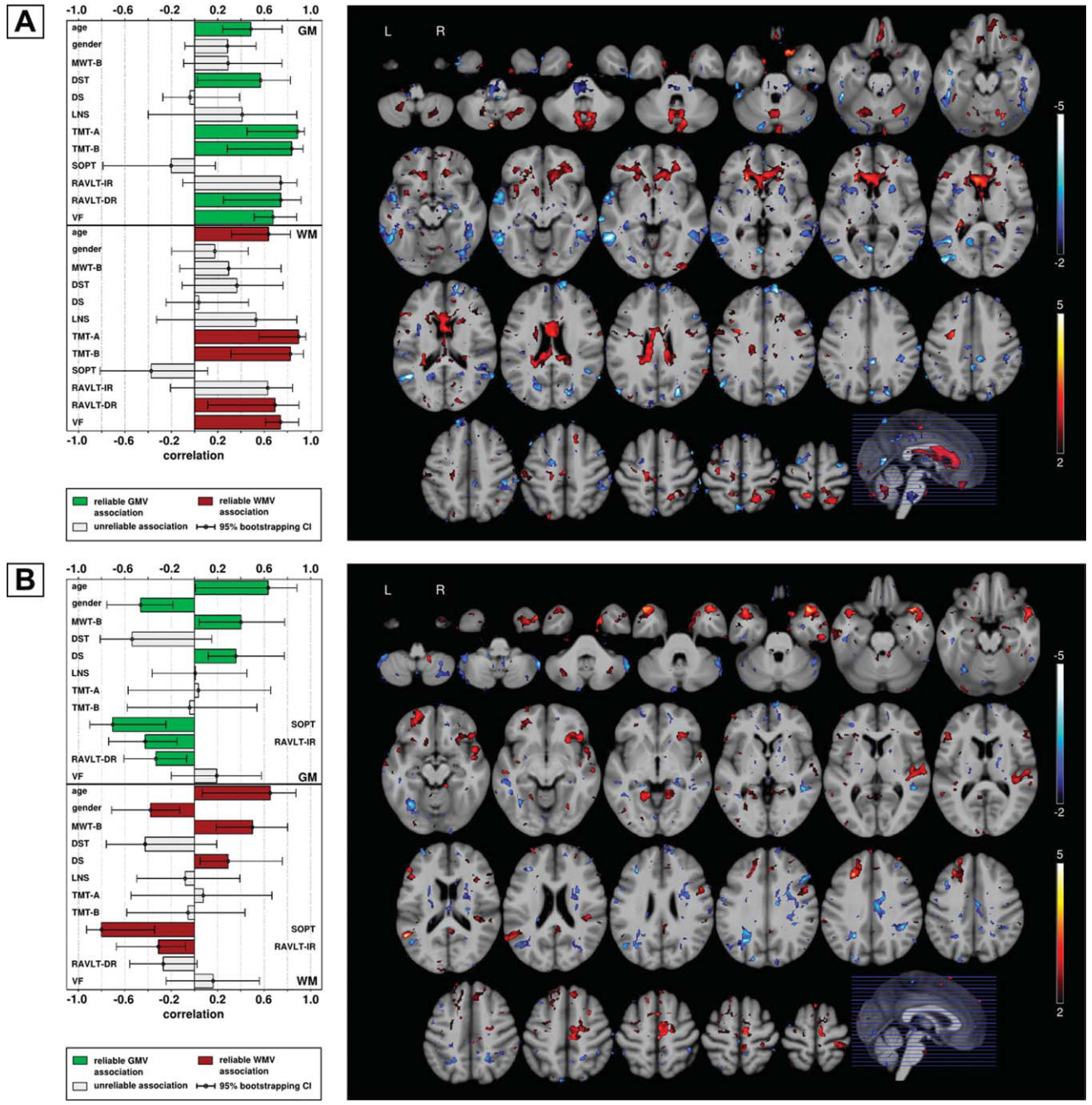

Figure 4.

Latent variables 1 and 3 of the within-group ARMS-NT analysis. See the legend of Figure 2 for a description of the left and right parts of the figure and Table II for the abbreviations of neuropsychological tests.

the ARMS obtained from the same study population [Koutsouleris et al., 2010b], the present findings suggest that the altered brain–cognition associations found in the established illness extend to the ARMS for psychosis. However, the explicit contribution of the current analysis is that these risk-related alterations are not limited to associations between cognitive set-shifting and fronto-callosal, cerebellar, and parietal brain structures, but involve much broader, cross-domain neurocognitive profiles as well as complex patterns of volumetric correlations.

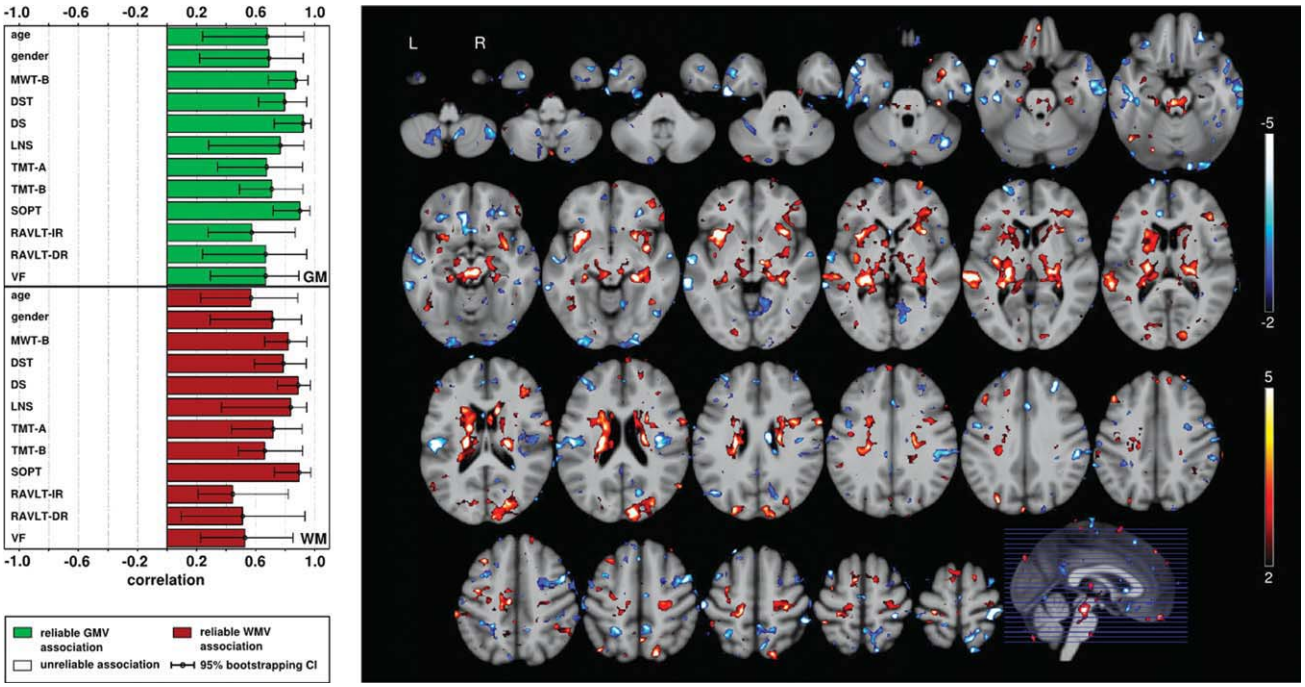

Figure 5.

Latent variable I of the within-group ARMS-T analysis. See the legend of Figure 2 for a description of the left and right parts of the figure and Table II for the abbreviatons of neuropsychological tests.

Furthermore, the PLS method extended our previous results by revealing that our HC group's neurocognitive profiles were mainly confined to verbal measures (Fig. 2A–C). In contrast, the ARMS group showed a broader neurocognitive profile, including also processing speed and executive functions (Fig. 3A). This cross-domain involvement was even more pronounced in the ARMS-T group; in that it affected the whole range of neurocognitive measures (see Fig. 5). Moreover, the current analysis revealed that the HC group's neuroanatomical saliences were rather diffusely distributed across cortical and subcortical structures (Fig. 2A–C). Conversely, the ARMS group's neuroanatomical patterns primarily mapped to prefrontal, limbic, temporal, perisylvian, and subcortical structures, including cortico-cortical and subcortico-cortical WM tracts (Fig. 3A,B). This localization of neuroanatomical loadings to these brain regions was most expressed in the ARMS-T group.

More specifically, LV1 of the ARMS model expressed a profile of broad, cross-domain neuropsychological involvement. This profile correlated (1) positively with prefrontal, limbic and paralimbic volumes, the intra- and interhemispheric cortico-cortical WM tracts (superior longitudinal fascicle, corpus callosum) and (2) negatively with occipito-temporo-parietal GMV. Furthermore, LV1 showed a reliable age- and gender covariation, meaning that low-performing, younger males had *less* volume than high-performing, older female subjects in voxels with positive loadings. This relationship was reversed in voxels with negative loadings. In keeping with our second hypothesis, the inner product analysis (Fig. 1A) revealed that this pattern was largely driven by the ARMS-L group, suggesting that LV1 was linked to an ultra-high risk for psychosis.

A similar neurocognitive profile was observed in the LV1 of the ARMS-T model (see Fig. 5) consisting of generalized, cross-domain neurocognitive involvement with an emphasis on working memory/verbal IQ and an even stronger age/gender covariation effect. Furthermore, the respective singular image expressed a spatial separation of positive and negative saliences similar to the LV1 singular image of the ARMS model. However, the LV1 singular image of ARMS-T consisted of highly reliable positive saliences particularly in the insular and limbic structures, the basal ganglia and neighboring/associated WM tracts, as well as of highly reliable negative saliences distributed across the temporal, prefrontal, parietal, and occipital cortices. As shown by the inner product analysis, this singular image specifically predicted the differential effect of between-group LV1 in the ARMS-NT vs. ARMS-T omnibus analysis (Fig. 1B). However, it did not solely drive the differences between HC and ARMS subjects as the respective singular image of the nonconversion group showed an almost equal correlation with

between-group LV1 in the HC vs. ARMS omnibus test (Fig. 1A). This observation suggests that brain–cognition associations specifically linked to disease transition may be differentiated from covariance patterns related to a vulnerability for psychosis-like experiences [Cornblatt et al., 1997; Lencz et al., 2006].

Taken together, three conclusions may be drawn. First, a convergent mapping from a broad profile of neurocognitive functions to a specific set of prefrontal, perisylvian, temporal, and subcortical structures distinguished the ARMS from HC subjects. This neurocognitive-neuroanatomical convergence was particularly expressed in the conversion group that showed a strong positive association between cross-domain neuropsychological measures and subcortical, limbic, and paralimbic structures. This observation agrees with several lines of evidence, including (1) the established involvement of these brain structures in a pattern of volumetric abnormalities characterizing the ARMS [Borgwardt et al., 2007, 2008; Job et al., 2005; Koutsouleris et al., 2009b; Meisenzahl et al., 2008b; Pantelis et al., 2003] as well as overt psychosis [Honea et al., 2005; Pantelis et al., 2005], (2) correlations between hippocampal volume and delayed verbal recall in ARMS-L, but not ARMS-E or HC subjects [Hurlemann et al., 2008], (3) strong positive correlations between thalamic volumes and RAVLT-IR performance in genetic high-risk individuals with a subsequent disease transition (Lymer et al., 2006), (4) disruptions of fronto-temporo-limbic connectivity [Nakamura et al., 2005] and structural abnormalities of the caudate nuclei [Levitt et al., 2002, 2004] relating to cognitive dysfunction in schizotypal personality disorder, and (5) altered associations between prefronto-temporo-limbic and subcortical volumes (and interconnecting WMV) and executive/memory functions in schizophrenia [Bonilha et al., 2008; Cocchi et al., 2009; Crespo-Facorro et al., 2007b; Gur et al., 2000; Laywer et al., 2006; Nakamura et al., 2008; Nestor et al., 2002; Premkumar et al., 2008; Pérez-Iglesias et al., 2010; Rüsch et al., 2007; Sanfilipo et al., 2002; Szeszko et al., 2002]. In particular, our findings are consistent with the brain–cognition study of Nestor et al. [2002], which was the first to use PLS for the analysis of multivariate mappings from neurocognitive to neuroanatomical measures in chronic schizophrenic patients. Their PLS analysis revealed associations between prefronto-temporal regions of interest and neurocognitive variables measuring categorization abilities (temporal and paralimbic structures) as well as working memory and mental set-shifting functions (frontal lobes).

Second, the neuroanatomical separation of positive and negative saliences in the ARMS-specific brain–cognition patterns, which was particularly expressed by the conversion group, suggests a differential neurocognitive involvement of neural structures. In the light of the considerable neural plasticity observed in early adulthood [Pantelis et al., 2005; Rapoport and Gogtay, 2008; Shaw et al., 2008], one speculative interpretation may be that positive brain–cognition correlations reflect the biological processes associated with the risk for conversion to psychosis, while negative associations result from continuous compensatory processes, which lead to an augmentation of GMV and WMV in the associated brain structures, e.g., through an increase in synaptic density [Murray et al., 2010; Ragland et al., 2004; Rüsch et al., 2007]. This interpretation may be further supported by findings of volumetric increments within paralimbic, inferior temporal, parietal and occipital brain regions of converters vs. non-converters [Borgwardt et al., 2007] and first-episode patients vs. HC [Cocchi et al., 2009], as well as by reports of "counterintuitive" negative brain–cognition correlations in schizophrenic patients vs. HC [Cocchi et al., 2009; Rüsch et al., 2007; Sanfilipo et al., 2002]. Alternatively, the spatial separation of positive and negative brain–cognition correlations may result from an abnormal maturational trajectory leading to distinct patterns of excessive and defective synaptic pruning during different critical periods of brain development [Harris et al., 2004; Keshavan et al., 1994; Lacerda et al., 2007; Pantelis et al., 2005; Rapoport and Gogtay, 2008].

Third, these conclusions have to be interpreted with respect to the age and gender dependencies of the risk-specific brain–cognition associations. This finding of a double covariation agrees with (1) reports of sexually dimorphic brain abnormalities in the ARMS and established psychosis [Davatzikos et al., 2005; Goldstein et al., 2002; Koutsouleris et al., 2009b; Narr et al., 2003], with a particular involvement of younger, male compared to older, female patients [Narr et al., 2003] and (2) studies showing a stronger cognitive impairment of male vs. female patients [Goldstein et al., 1998, 1994; Walder et al., 2007].

These observations should be further explored in future studies of larger samples that prospectively combine neuroanatomical and neuropsychological measurements in order to clarify the trajectories of brain–behavior associations in emerging psychosis. Finally, we demonstrated that multivariate statistical methods have the potential to unveil complex links between brain and behavior by dissecting their associations into interpretable covariance components. Therefore, these techniques may be of broader interest to the field as they may allow deconstructing the multifaceted psychiatric phenotypes into their distinct neural components.

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