White matter alterations related to P300 abnormalities in individuals at high risk for psychosis: an MRI–EEG study

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Background: Psychosis onset is characterized by white matter and electrophysiologic abnormalities. The relation between these factors in the development of illness is almost unknown. We studied the relation between white matter volumes and P300 in prodromal psychosis. **Methods:** We assessed white matter volume (detected using magnetic resonance imaging) and electrophysiologic response during an oddball task (P300) in healthy controls and individuals at high clinical risk for psychosis (with an “at-risk mental state” [ARMS]). **Results:** We included 41 controls and 39 patients with an ARMS in our study. A psychotic disorder developed in 26% of the ARMS group within the follow-up period of 2 years. The P300 amplitude was significantly lower in the ARMS group than in the control group. The ARMS group showed reduced volume of white matter underlying the left superior temporal gyrus and the left superior frontal gyrus and increased volume of white matter underlying the right insula and the right angular gyrus compared with controls. Relative to individuals who did not later become psychotic, the subgroup in whom psychosis subsequently developed had a smaller volume of white matter underlying the left precuneus and the right middle temporal gyrus and increased volume in the white matter underlying the right middle frontal gyrus. We observed a significant interaction in the right middle frontal gyrus: white matter volume was negatively associated with P300 amplitude in the ARMS group and positively associated with P300 amplitude in the control group. **Limitations:** The voxel-based morphometry method alone cannot determine whether abnormal white matter volumes are due to an altered number of axonal connections or decreased myelination. **Conclusion:** P300 abnormalities precede the onset of psychosis and are directly related to white matter alterations, representing a correlate of an increased vulnerability to disease.

Introduction

A number of studies have shown that patients with schizophrenia display a smaller than normal auditory P300 over the midline central and parietal scalp electrode locations (for a meta-analysis, see Jeon and colleagues¹). Auditory P300 abnormalities are already evident at the time of the initial onset of illness^{2–4} and are related to the duration of untreated psychosis.⁵ Despite the potential role of P300 abnormalities in the etiopathology of schizophrenia, its cerebral origin is not clear as it involves the complex summation of activity from multiple

brain regions, particularly the various association areas of the cerebral cortex.⁶ P300 may have multiple brain generators, including the loci in the temporal, frontal and parietal lobes.⁴ Consistently, studies in patients with chronic schizophrenia have pinpointed an association between P300 and structural alterations in prefrontal⁷ and temporal^{4,8,9} areas. However, the relation between P300 abnormalities and brain structure in the development of the disease is still unknown. One way to address this point is to investigate the prodrome to schizophrenia. Individuals with an “at-risk mental state” (ARMS) present with prodromal symptoms of psychosis and have a very high

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risk for the disease developing within the next 2 years.¹⁰ The ARMS is characterized by poor psychosocial functioning¹¹ and neurocognitive impairments.¹² Interestingly, 3 recent independent studies of individuals at enhanced risk for psychosis have confirmed that P300 abnormalities are already evident in the prepsychotic phases.^{13–15} P300 can index a neurobiologic vulnerability to schizophrenia, in line with other studies showing P300 abnormalities in relatives of individuals with psychosis.^{16,17} On the other hand, neuroimaging studies have indicated that patients at high risk for psychosis show alterations in white matter^{18,19} volume in fronto-temporal regions. In particular, the first study exploring white matter in the prepsychotic phases found reduced temporal lobe volume in patients at increased clinical risk for psychosis.¹⁸ Another study found that the ARMS patients who later became psychotic had larger volumes of white matter in the frontal lobe.¹⁹ These alterations resemble those observed during the established phases of the illness but are less marked.²⁰ White matter abnormalities in schizophrenia research have been interpreted as disturbed connectivity of neural networks (“disconnectivity hypothesis”²¹), affecting prefrontal–temporolimbic connections,^{22,23} cortico–cerebellar–thalamic–cortical circuits^{24,25} and interhemispheric connectivity.²⁶ In line with such theories, fronto-temporal disconnectivity during cognitive functioning has been recently observed in ARMS patients.^{27,28} Disruption of white matter tracts may thus alter the electrophysiologic response and perturb brain connectivity during the prepsychotic phases. A combined event-related potential (ERP) and magnetic resonance imaging (MRI) study in healthy adults has confirmed significant correlations between P300 measures and white matter contractions,²⁹ whereas a recent study involving patients presenting with a first episode of psychosis has found specific correlations between anisotropy values and P300 measures.³⁰ Although there is independent evidence indicating both P300 and white matter alterations in patients at risk for psychosis, no formal study has properly tested the putative relation of these factors during the prepsychotic phases.

To our knowledge, this is the first study to address the relation between white matter volumes and P300 in prodromal psychosis. To address this, we have employed voxel-based morphometry (VBM) and electrophysiology measures (P300). Although the VBM technique was originally developed to assess grey matter abnormalities, a number of recent imaging studies have employed the method to evaluate white matter volume in healthy and clinical populations. On the basis of the evidence above, we predicted that ARMS patients would show abnormal P300 amplitude and regional white matter volume compared with controls, that such abnormalities would be directly related and that these alterations would predict later transition to psychosis.

Methods

Participants

We recruited individuals meeting Personal Assessment and Crisis Evaluation (PACE) criteria for ARMS³¹ from Outreach and Support in South London (OASIS).³² The diagnosis was

based on assessment by 2 experienced clinicians using the Comprehensive Assessment for the ARMS (CAARMS)³³ and a consensus meeting with the clinical team. An individual can meet criteria for ARMS in 1 or more of 3 ways: 1) a recent decline in function coupled with either schizotypal personality disorder or a first-degree relative with psychosis, 2) attenuated positive symptoms and 3) a brief psychotic episode of less than 1 week’s duration that resolves without antipsychotic medication. Transition to psychosis was defined according to the criteria in the CAARMS (i.e., presence of at least 1 positive psychotic symptom at high severity for more than 1 week). The ARMS group was representative of the local population of people presenting with an ARMS in terms of age, sex, race and duration and intensity of symptoms. We excluded patients with a history of neurologic disorders or if they met the DSM-IV criteria for a substance-abuse or dependence disorder.

We recruited healthy volunteers from the same geographic area as participants in the ARMS group via advertisements in the local media. Inclusion criteria were no personal history of psychiatric symptoms (as assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders, nonpatient edition [SCID-NP]³⁴), no substance dependence or abuse, no use of psychotropic medications, no medical illness and no family history of psychiatric illness (as assessed by the SCID-NP³⁴).

We evaluated handedness using the Lateral Preferences Inventory.³⁵ Informed consent was collected from all participants, and the protocol was approved by the local Ethical Committee (Institute of Psychiatry).

Clinical measures

The severity of symptoms in the clinical groups was assessed at the time of scanning using the CAARMS³³ and the Positive and Negative Symptom Scale (PANSS).³⁶ Premorbid intelligence was assessed using the National Adult Reading Test (NART).³⁷ We tested the effect of group on demographic and clinical measures using analyses of variance for parametric variables, and Mann–Whitney *U* tests were used to compare the ARMS and control groups for nonparametric variables after checking for equality of variance with the Levene test.

Magnetic resonance imaging

Image acquisition

Images were acquired on a 1.5-T General Electric Signa LX system using a standard quadrature head coil at the Maudsley Hospital, London, UK. A 3-dimensional *T*₁-weighted inversion recovery prepared spoiled gradient recalled echo (SPGR) sequence was performed with the following parameters: pure coronal orientation, 128 slices, slice thickness 1.5 mm, echo time (TE) 5.1 ms, repetition time (TR) 17.9 ms, inversion time (TI) 450 ms, flip angle 20°, matrix 256 × 144 over a field of view (FOV) of 22 × 20 cm, reconstructed to a 256 × 256 matrix over a FOV of 22 × 22 cm, number of excitation (NEX) 0.75.

Image analysis

Structural images were preprocessed using optimized voxel-based morphometry (VBM) implemented with Statistical

Parametric Mapping software (SPM5) running under MATLAB version 7.0. Voxel-based morphometry is a whole-brain, unbiased, semiautomated technique for characterizing regional cerebral differences in structural MRI scans.³⁸ First, structural images were segmented to extract white matter and then normalized to an asymmetric template in Montreal Neurological Institute (MNI) stereotactic space in a recursive fashion. Image segmentation incorporated an intensity nonuniformity correction to account for smooth intensity variations caused by gradient distortions and different positions of cranial structures within the MRI coil.³⁸ We added a further step to ensure that the total amount of white matter in each voxel was conserved before and after spatial normalization.³⁹ This modulation step involved multiplying the spatially normalized white matter by its relative volume before and after spatial normalization. The resulting white matter images were finally smoothed with an 8-mm isotropic Gaussian kernel. Smoothing is required to compensate for the inexact nature of spatial normalization and to maximize the chance that regional effects are expressed at a spatial scale where homologies in structural anatomy exist across participants. After smoothing, each voxel represents the local average amount of white matter in the region, the size of which is defined by the smoothing kernel. We performed an analysis of variance (ANOVA) to identify significant differences in white matter volume across groups; age and sex were included as covariates of no interest to reduce the potential impact of these variables on the findings.⁴⁰ Inferences were made using a statistical threshold of $p < 0.05$, family wise error (FWE)-corrected. Significant foci were anatomically localized using the standard atlas of Talairach and Tournoux.

P300 paradigm

Voluntary and automatic attention yield distinct scalp-recorded ERPs, referred to as the P3b (target detection) and the P3a (novelty detection), respectively. The P3b is a positive-going ERP with parietal maximum amplitude and a peak latency of about 300–600 ms in young adults. It is typically elicited in tasks wherein 2 types of stimuli of unequal probability are presented, and attention is to be paid to the infrequent ones, such as the oddball tasks.⁴¹ In this study, we obtained the P300 (P3b) with a standard auditory oddball paradigm⁴² in a subsample of the ARMS ($n = 28$) and control groups ($n = 13$). Stimuli were 480 dB tones, with a 2-second (standard deviation [SD] 0.2 s) interstimulus interval presented through bilateral intra-aural earphones. Eighty percent of the tones were “nontargets” of 1000 Hz and 20% were “targets” of 1500 Hz in a random sequence. We instructed participants to keep their eyes open and press a button in response to target tones only. Electroencephalography (EEG) data were collected from 64 scalp sites according to the 10/20 International System and were grounded at Fpz using sintered electrodes in a cap.¹⁴ Vertical and horizontal electro-oculographs monitored eye movements. Data were continuously digitized at 1000 Hz with a 0.05- to 100-Hz band-pass filter (24 dB/octave roll-off). Impedances were kept below 5 k Ω . We employed a neuroscan linear regression procedure to minimize ocular artifacts.⁴³ The continuous EEG recording

was epoched (–100 to 700 ms), baseline-corrected using the prestimulus interval (–100 to 0 ms), band-pass filtered (0.05 to 45 Hz) and averaged for targets and nontargets separately.⁴² The P300 was defined as a positive waveform generated by the target tones and peaking between 280 and 500 ms poststimulus. The P300 results of a larger sample have been previously published.¹⁴ We analyzed between-group differences in P300 amplitude with independent t tests ($p < 0.05$).

Integration of VBM and P300 measures

To explore the correlation between the white matter volume and P300 amplitude, we entered P300 values as covariates in the between-group VBM analysis. Results were reported at $p < 0.05$, FWE-corrected. We also completed a post hoc analysis of potential interactions between white matter volumes and P300 amplitude by extracting the individual volumes and testing them in a general linear regression model (dependent variable P300 amplitude, independent variable regional grey matter volume) in SPSS ($p < 0.05$). We used the Cook distance test to assess the effect of potential outliers on the correlations.

Results

Participant characteristics

Baseline characteristics

We included 41 healthy controls and 39 patients with an ARMS in our study. All participants were right-handed and native English speakers. The 2 groups were matched on socio-demographic variables, including age, premorbid IQ, laterality quotient, race and years of education. The ARMS group showed higher unemployment rates than the control group. As expected, patients at clinical risk for psychosis showed higher scores on the PANSS subscales compared with controls. When subsamples of the original cohort were selected for specific imaging analysis, we carefully checked that participants in the ARMS and control groups were matched on sociodemographic characteristics. Clinical and sociodemographic characteristics of all participants are displayed in Table 1.

Longitudinal outcomes

The sample of patients at risk for psychosis received standard clinical management through the OASIS service, irrespective of participation in this study. About 80% of the ARMS group received cognitive behavioural therapy, and about 46% received low-dose atypical antipsychotic medication. The sample was followed up clinically by the OASIS service, and 10 patients (26%) experienced a psychotic episode within the follow-up period of 2 years (ARMS with transition = ARMS-T; ARMS without transition = ARMS-NT; Table 2).

Electrophysiologic results

The P300 amplitude (PZ electrode) was significantly lower in the subsample of patients in the ARMS group ($n = 28$, mean 9.72, SD 7.08 μ V) than in the control group ($n = 13$, mean 13.62, SD 4.92 μ V; $t_{39} = 2.041$, $p = 0.049$, Fig. 1). No significant

difference in P300 amplitude between ARMS-T and ARMS-NT participants was observed (mean P300 amplitude 10.22, SD 7.71 μ V in the ARMS-T group v. 7.89 μ V, SD 3.98 in the ARMS-NT group; $t_{26} = 1.09$, $p = 0.61$).

Voxel-based morphometry results

ARMS versus controls

At baseline, there were significant white matter volumetric differences between participants at high risk for psychosis ($n = 39$) and healthy controls ($n = 41$). Relative to the control group, the ARMS group showed a smaller volume of white matter underlying the left superior temporal gyrus and the left superior frontal gyrus. In addition, the ARMS group showed an increased volume of white matter underlying the right insula and the right angular gyrus compared with the control group (Table 3, Fig. 2).

ARMS-T versus ARMS-NT

At baseline, there were significant white matter volumetric differences between participants who were at high risk according to their clinical outcome at follow-up. Relative to the ARMS-NT subgroup ($n = 29$), the ARMS-T subgroup ($n = 10$) had a smaller volume of white matter underlying the left pre-cuneus and the right middle temporal gyrus and increased volume of the white matter underlying the right middle frontal gyrus (Table 3).

Voxel-based morphometry-P300 results

Whole sample

There was a positive correlation ($R = 0.36$, $F_{1,39} = 5.74$, $p = 0.023$) between white matter volume of the right genu of the corpus callosum (MNI space $x, y, z = 2, 24, -4$; $K_E = 97$,

$Z = 4.93$) and P300 amplitude across the entire subsample of participants who underwent this procedure (ARMS group $n = 28$, control group $n = 13$). The correlation survived correction after the removal of potential outliers as identified with the Cook distance test ($R = 0.35$, $F_{1,39} = 4.85$, $p = 0.031$; Fig. 3). No negative correlations between white matter volume and P300 amplitude were observed.

Controls

Across the subsample of control group participants ($n = 13$), there was a positive correlation ($R = 0.73$, $F_{1,11} = 12.75$, $p = 0.029$) between white matter volumes underlying the right middle frontal gyrus (MNI space $x, y, z = 30, 40, 22$; $K_E = 72$, $Z = 4.74$) and P300 amplitude. The correlation survived correction after the removal of potential outliers as identified with the Cook distance test ($R = 0.83$, $F_{1,11} = 19.41$, $p = 0.011$). No negative correlations between white matter volume and P300 amplitude were observed.

ARMS

Across the subsample of participants in the ARMS group ($n = 28$), there was a positive correlation ($R = 0.71$, $F_{1,26} = 26.41$, $p < 0.001$) between white matter volume in a cluster underlying the right supramarginal gyrus and extending in the right arcuate fasciculus (MNI space $x, y, z = 48, -46, 30$; $K_E = 108$, $Z = 4.57$) and P300 amplitude. The correlation survived correction after the removal of potential outliers as identified with the Cook distance test ($R = 0.65$, $F_{1,26} = 16.08$, $p = 0.021$; Fig. 3). No negative correlations between white matter volume and P300 amplitude were found.

Interactions

There was a significant P300 $\times$ white matter $\times$ group interaction

Table 1: Clinical and sociodemographic characteristics of study participants

Characteristic	Group; mean (SD)*		Test statistic	
	ARMS, $n = 39$	Control, $n = 41$	t	p value
Age, yr	24.49 (4.55)	25.88 (5.24)	1.27	0.21
Premorbid IQ	98.66 (10.27)	102.33 (6.87)	1.75	0.08
Laterality quotient	82.07 (29.91)	80.82 (18.17)	-0.20	0.84
Years of education	13.00 (2.15)	14.40 (3.18)	1.24	0.19
PANSS score				
Positive	14.83 (4.60)	7.00 (0)	-9.16	< 0.001
Negative	8.90 (2.53)	7.00 (0)	-4.03	< 0.001
General	28.43 (9.07)	16.00 (0)	-7.37	< 0.001
Total	52.17 (12.60)	30.00 (0)	-9.47	< 0.001
Race, no. (%)				
White (British)	20 (51.28)	25 (60.98)	0.76	0.50
Other	19 (48.72)	16 (39.02)		
Sex, no. (%)				
Male	24 (61.54)	33 (80.49)	3.50	0.08
Female	15 (38.46)	8 (19.51)		
Employment, no. (%)				
Unemployed or student	24 (61.54)	12 (29.27)	8.41	0.007
Employed	15 (38.46)	29 (70.73)		

ARMS = at-risk mental state; PANSS = Positive and Negative Symptom Scale;* SD = standard deviation.

*Unless otherwise indicated.

in a cluster underlying the right middle frontal gyrus (MNI space $x, y, z = 30, 40, 22$; $K_E = 79$, $Z = 4.38$, $p = 0.041$). Post hoc analysis showed that in this region, white matter volume was

Table 2: Clinical management of the patients with at-risk mental state for psychosis, $n = 39$

Phase; management	No. (%) [*]
Assessment phase	
Source of referral	
Primary care	15 (38.46)
Secondary care	24 (61.54)
Comorbid diagnosis	
Absent	12 (30.77)
Present	27 (69.23)
Clinical measures, mean (SD)	
GAF	56.59 (11.98)
CAARMS	
Thought disorders	3.67 (1.26)
Perceptual disorders	2.62 (1.76)
Speech disorders	1.82 (1.47)
Intervention phase	
Antipsychotic prescribed	
Yes	18 (46.15)
No	21 (53.85)
Cognitive behavioural therapy	
Yes	32 (82.05)
No	7 (17.95)
Outcome	
Transition to psychosis	
Yes	10 (25.64)
No	29 (74.36)

CAARMS = Comprehensive Assessment for the At-Risk Mental State;³⁹ GAF = Global Assessment of Functioning; SD = standard deviation.
^{*}Unless otherwise indicated.

positively correlated with P300 amplitude in the control group and negatively correlated in the ARMS group (Fig. 3).

Discussion

The goal of the present study was to address the relation between white matter alterations and P300 abnormalities in patients at high clinical risk for psychosis. Using 2 different neuroimaging protocols in the same patients is logistically difficult, and to our knowledge, no investigation has ever addressed this issue in the prodromal phases of psychosis. We found that participants in the ARMS group had abnormal white matter volumes, with temporoparietal and prefrontal alterations being associated with transition to psychosis. The ARMS group also had lower P300 amplitude than the control group. We observed significant correlations between white matter and P300 amplitude in the temporo-parietal junction and in the prefrontal cortex.

In line with our preliminary hypothesis, the ARMS group showed reduced volume of white matter underlying the left superior temporal gyrus and the left superior frontal gyrus compared with the control group. The only available VBM study of white matter volume comparing high-risk patients and controls found white matter reductions in the temporal lobe of the patient group.¹⁸ Our results further confirm that the temporal lobe plays a crucial role in the prodromal phases of psychosis. In addition, to our knowledge, we showed for the first time concurrent temporal and prefrontal white matter reductions on the left side. On the basis of the literature indicating abnormalities in brain connectivity between the superior temporal gyrus and the prefrontal cortex of the ARMS group,²⁸ our findings may reflect an alteration of white matter volume in regions carrying fibres between the

Fig. 1: Extended international 10–20 montage used for electroencephalography recording (left). We observed decreased P300 amplitude (PZ electrode) in the subsample of patients in the at-risk mental state (ARMS) group ($n = 28$) compared with the subsample in the control group ($n = 13$) who underwent the standard auditory oddball task (right; $p = 0.017$). SE = standard error.

left frontal and left temporal lobes.¹⁹ Such abnormalities are consistent with structural and functional imaging studies in patients at risk for psychosis.^{44–46} In support of these findings, previous diffusion tensor imaging (DTI) studies in patients with schizophrenia have confirmed reduced anisotropy in the frontal cortex,^{47–50} the anterior cingulum^{51,52} and the temporal lobe.^{20,53}

The ARMS group also showed a reduced P300 amplitude compared with controls, in line with our previous results in a larger sample¹⁴ and with other studies in patients at risk for psychosis.^{15,54} Functionally, the P300 reflects the summation of multiple, simultaneously occurring cognitive and brain processes that are linked to attentional resource allocation and memory-updating operations in the brain.⁶ Consequently, the observed P300 abnormalities in the ARMS group are consistent with data from behavioural studies indicating impaired performance on tasks that engage attention and executive

processes.¹² Given the cross-sectional design of the present study, it is not possible to determine whether in prodromal psychosis grey matter abnormalities lead to electrophysiologic alterations or vice versa. Nevertheless there is growing evidence from neuroimaging and postmortem studies for primary subtle changes of structural (subcortical) macro-circuit connectivity in patients with schizophrenia that may lead to secondary electrophysiologic abnormalities. For example, several studies have shown a significant reduction of oligodendroglial cells and ultrastructural alterations of myelin in patients with schizophrenia. Similarly, there is also growing evidence for abnormal expression of myelin-related genes in patients with schizophrenia (for a review, see Konrad and Winterer⁵⁵).

Our finding of significant associations between white matter volume and electrophysiologic measures during the odd-ball task is in line with our principal hypothesis. First, within

Table 3: Foci of white matter abnormalities in patients at clinical risk for psychosis ($p < 0.05$, FWE-corrected)

Group comparison; brain region	No.*		Side	MNI coordinate			No. voxels	Z score
	First group	Second group		x	y	z		
Controls > ARMS	41	39						
Superior temporal gyrus			Left	-56	-38	20	102	3.96
Superior frontal gyrus			Left	-18	32	48	29	3.34
ARMS > controls	41	39						
Insula			Right	46	-12	18	114	3.94
Angular gyrus			Right	42	-62	36	89	3.86
ARMS-NT > ARMS-T	29	10						
Precuneus			Left	-16	-62	50	257	4.29
Middle temporal gyrus			Right	40	-70	26	45	3.66
ARMS-T > ARMS-NT	10	29						
Middle frontal gyrus			Right	24	36	38	30	3.58

ARMS = at-risk mental state; ARMS-NT = subgroup of patients without transition to psychosis; ARMS-T = subgroup of patients with transition to psychosis; FWE = family-wise error; MNI = Montreal Neurological Institute.

*Sample size for the first and second group in the specified comparison.

Fig. 2: Cross-sectional analysis of white matter abnormalities between the control and the at-risk mental state (ARMS) groups.

Fig. 3: Correlation between white matter volume and P300 amplitude across the whole sample ($n = 41$, $R = 0.35$, $F_1 = 4.85$, $p = 0.032$; **top**), in the subsample of patients in the at-risk mental state (ARMS) group who underwent the standard auditory oddball task ($n = 28$, $R = 0.71$, $F_1 = 26.41$, $p < 0.001$, **middle**) and in the group $\times$ P300 $\times$ white matter interaction (ARMS = 28, controls = 13; $Z = 4.38$, $p = 0.029$, **bottom**).

the whole sample, we uncovered a positive correlation between the white matter volume of the genu of the corpus callosum and P300 amplitude: a reduction in white matter was associated with reduction in P300 amplitude. The corpus callosum is the major interhemispheric commissure between neocortical association regions; callosal transfers play a crucial role in interhemispheric communication and integration, and abnormalities of the corpus callosum can affect P300 amplitude. The corpus callosum size can reflect the myelination of interhemispheric fibres, which would probably influence interhemispheric communication and, therefore, P300 measures. In line with these neuroanatomic considerations, 2 independent studies found that P300 amplitude and latency were positively correlated with the corpus callosum volume.^{29,56} There is further evidence indicating a positive correlation between anisotropy values of the genu and P300 measures during a continuous performance test.³⁰

Second, we uncovered a positive association between P300 amplitude and the white matter volume underlying the right supramarginal gyrus extending into the right arcuate fasciculus. Such correlation was observed in the ARMS group but not in the control group. Although the intracerebral origins of the P300 (and its components P3a and P3b) are not clear, the main regions consistently implicated include the temporal-parietal junction, medial temporal complex and lateral prefrontal cortex.^{57,58} In particular, the P3b-like potential (as the one employed in this study) engages the multimodal association cortex, including the supramarginal gyrus, which constitutes an associative area that receives auditory, visual and somatosensory inputs.⁵⁷ Previous auditory oddball fMRI-ERP studies clearly indicated the supramarginal gyrus is the main generator of the scalp-recorded P3b.⁵⁹ Lesion studies confirmed that discrete damage in the temporoparietal junction, including the supramarginal gyrus, results in severe reduction of P3b activity at posterior scalp sites in both the auditory⁶⁰ and somatosensory modalities.⁶¹ Animal studies further support the notion that the posterior scalp P3b component marks activity in the supramarginal gyrus during engagement of early attention and memory processes.⁵⁷ Previous MRI-EEG studies have shown that superior temporal gyrus volume is associated with smaller P300 in patients with chronic⁸ or first-episode⁴ schizophrenia. To our knowledge, our study is the first to demonstrate that a significant correlation between supramarginal white matter volume and P300 is already evident during the prodromal phases of psychosis. This finding is in line with recent theories suggesting that P300 amplitude alterations in patients with schizophrenia are associated with early temporo-parietal maturation abnormalities followed by further functional impairments later in life.¹⁵

Third, we found a significant group $\times$ white matter $\times$ P300 interaction in the right middle frontal gyrus, with white matter volume being correlated with P300 in the control group (positive correlation) and in the ARMS group (negative correlation). Previous functional imaging studies support the involvement of the dorsolateral prefrontal cortex during the oddball task⁶² and in the generation of P300 amplitude.⁶³ A recent EEG-fMRI study investigating the localization and activities of the P300 generators further confirmed the engage-

ment of the middle frontal gyrus in P300.⁶⁴ Consequently, it is possible that the integrity of this region is fundamental to the physiologic generation of P300. There is also consistent neuroimaging evidence indicating that the prefrontal cortex is already altered in the ARMS group.⁴⁴

Finally, we have attempted to identify the core abnormalities underlying transition to psychosis.⁶⁵ Thus, we have compared the ARMS-T and the ARMS-NT subgroups. The ARMS-T subgroup showed robust volumetric white matter differences compared with the ARMS-NT subgroup, with white matter reductions in the parietal lobule and in the middle temporal gyrus and white matter increases in the right middle frontal gyrus. Previous MRI studies of ARMS groups have found grey matter reductions in parietal and temporal areas in cohorts of individuals at high risk for psychosis (for a review, see Wood and colleagues⁴⁶). These structural abnormalities can be interpreted as reflecting an active pathologic process underlying the transition to psychosis. Given the interaction that we observed in the middle frontal gyrus, it is possible to speculate that the white matter increases in the ARMS-T group are associated with reduced P300 amplitude. Although we did not find P300 differences between the ARMS-T and ARMS-NT subgroups, we cannot exclude that in a larger sample size we would have been able to detect significant amplitude differences underlying transition to psychosis. White matter increases in ARMS-T groups have been previously reported to be a compensatory response to an abnormal reduction in grey matter volume.¹⁹ Such increases could also be considered reflective of increased prefrontal cortical folding, as measured by the gyrification index, which can be seen as an indirect measure of axonal connectivity.⁶⁶ Increased prefrontal gyrification has been demonstrated in patients with schizophrenia⁶⁷ and has been shown to be predictive of transition to psychosis in high-risk cohorts.⁶⁸

Limitations

Limitations of the present study are well acknowledged. Voxel-wise structural image analysis is a method of looking for anatomic variations without prior hypotheses about the location and extent of those variations. However, using the VBM method alone, we could not tell if the abnormal white matter volumes were due to an altered number of axonal connections or decreased myelination. In fact, the amplitude and scalp topography of P300 is related to the number, size, location and orientation of the neural generators and to the strength and synchrony of the neural response of each generator. Disease can reduce P300 amplitude by weakening the neural generator response or by altering the connectivity between different generators. Diffusion tensor imaging or the application of tractography to the abnormal white matter regions identified in the present study can provide more detailed information about the tracts and the connectivity within white matter.

Conclusion

P300 abnormalities precede the psychosis onset and are

directly related to white matter alterations, representing a correlate of an increased vulnerability to disease.

Competing interests: None declared.

Contributors: Dr. Fusar-Poli designed the study and wrote the article; all other authors reviewed the article. All authors acquired the data, which Drs. Fusar-Poli and Crossley analyzed. All authors approved publication of the article.

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