Neurobiological substrates of major psychiatry disorders: transdiagnostic associations between white matter abnormalities, neuregulin 1 and clinical manifestation

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Background: Schizophrenia, bipolar disorder and major depressive disorder are increasingly being conceptualized as a transdiagnostic continuum. Disruption of white matter is a common alteration in these psychiatric disorders, but the molecular mechanisms underlying the disruption remain unclear. Neuregulin 1 (NRG1) is genetically linked with susceptibility to schizophrenia, bipolar disorder and major depressive disorder, and it is also related to white matter. **Methods:** Using a transdiagnostic approach, we aimed to identify white matter differences associated with NRG1 and their relationship to transdiagnostic symptoms and cognitive function. We examined the white matter of 1051 participants (318 healthy controls and 733 patients with major psychiatric disorders: 254 with schizophrenia, 212 with bipolar disorder and 267 with major depressive disorder) who underwent diffusion tensor imaging. We measured the plasma NRG1-β1 levels of 331 participants. We also evaluated clinical symptoms and cognitive function. **Results:** In the patient group, abnormal white matter was negatively associated with NRG1-β1 levels in the genu of the corpus callosum, right uncinate fasciculus, bilateral inferior fronto-occipital fasciculus, right external capsule, fornix, right optic tract, left straight gyrus white matter and left olfactory radiation. These NRG1-associated white matter abnormalities were also associated with depression and anxiety symptoms and executive function in patients with a major psychiatric disorder. Furthermore, across the 3 disorders we observed analogous alterations in white matter, NRG1-β1 levels and clinical manifestations. **Limitations:** Medication status, the wide age range and our cross-sectional findings were limitations of this study. **Conclusion:** This study is the first to provide evidence for an association between NRG1, white matter abnormalities, clinical symptoms and cognition in a transdiagnostic psychiatric cohort. These findings provide further support for an understanding of the molecular mechanisms that underlie the neuroimaging substrates of major psychiatric disorders and their clinical implications.

Introduction

Schizophrenia, bipolar disorder and major depressive disorder have been separate diagnoses since the time of Kraepelin in the 1920s.[1] However, diagnostic categories based on presenting signs and symptoms in psychiatric disorders may not capture the fundamental underlying mechanisms of dysfunction.[2,3] Increasing evidence suggests that these 3 conditions overlap in terms of risk genes,[4] endocrine and metabolic markers,[5] brain structure and function,[6,7] clinical symptoms[8] and cognitive deficits.[9] As a result, there has

been increasing discussion in the psychiatric community about conceptualizing schizophrenia, bipolar disorder and major depressive disorder as major psychiatric disorders, a transdiagnostic continuum of disorders with common clinical characteristics.[10] Such a reconceptualization allows us to analyze the biological features of these diagnoses at multiple levels[11] and to explore symptom-specific/disease-general biological mechanisms.

White matter alterations are a common neurobiological abnormality in major psychiatric disorders.[7] Disruption of the white matter microstructure, detectable with diffusion

tensor imaging (DTI), can reflect compromises of myelin, the cytoskeletal structure or axonal density. Fractional anisotropy (FA) is a commonly used DTI metric for indexing white matter that can reflect many of the structural properties of white matter, such as axon density and degree of myelination.[12,13] Studies using DTI have found shared white matter abnormalities in schizophrenia, bipolar disorder and major depressive disorder.[14,15] Abnormal white matter is also related to clinical symptoms and cognitive function.[16,17] Despite such evidence, the molecular mechanisms underlying white matter alterations remain unclear, and few studies have taken a transdiagnostic approach to understanding these mechanisms.

The neural growth factor neuregulin 1 (NRG1) is a likely candidate for the molecular basis of white matter alteration in major psychiatric disorders. *NRG1* is a common susceptibility gene for schizophrenia, bipolar disorder and major depressive disorder,[18–21] indicating that NRG1 is involved in the pathogenesis of major psychiatric disorders. Increasing genetic evidence and animal models have also shown altered NRG1–ErbB signalling in the nervous system in the presence of major psychiatric disorders.[22–26] Furthermore, findings from recent animal and human studies suggest that NRG1 could affect white matter.[27–33] Animal studies have shown that NRG1 plays an important role in myelination and influences the development of white matter.[28,29] Human studies have found that NRG1 preferentially concentrates in the white matter;[30] genetic variation in *NRG1* is associated with white matter abnormalities (FA reduction) in psychiatric disorders.[31–33] Nevertheless, it is not clear whether there are transdiagnostic white matter alterations associated with NRG1 in psychiatric disorders; as well, the effect of NRG1-associated white matter abnormalities on common symptomatology and cognition is not well understood.

Our aim was to identify common transdiagnostic neuroimaging substrates of major psychiatric disorders with potential molecular mechanisms, and to clarify the clinical implications of those substrates. We assessed a large sample of patients with schizophrenia, bipolar disorder or major depressive disorder collected at a single site to characterize the relationship between plasma profile, brain structure and psychopathology. Specifically, we looked at plasma levels of NRG1-β1 (one of the isoforms of NRG1, which has the ability to pass the blood–brain barrier and has been used in many studies[34,35]), white matter assessed via DTI, and clinical symptoms and cognitive function. We hypothesized that abnormal white matter in major psychiatric disorders would be associated with NRG1 plasma levels, and that such NRG1-associated white matter abnormalities would be correlated with clinical symptoms and cognitive function in a transdiagnostic fashion.

Methods

Participants

The study was conducted at a single site and included 1061 participants aged 13 to 55 years (260 patients with schizophrenia, 213 with bipolar disorder, 269 with major depressive disorder and 319 healthy controls). All participants with schizophrenia, bipolar disorder or major depressive disorder were recruited from the inpatient and outpatient services at Shenyang Mental Health Centre and the Department of Psychiatry, First Affiliated Hospital of China Medical University, Shenyang, China. Healthy controls were recruited from the local community by advertisement. All participants were Chinese. All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Medical Science Research Ethics Committee of the First Affiliated Hospital of China Medical University (approval reference number [2012]25–1) and was consistent with the principles outlined in an internationally recognized standard for the ethical conduct of human research. After the study was thoroughly described to them, participants provided written informed consent (or their parents/guardians did, if they were younger than 18 years old).

All participants were evaluated by 2 trained psychiatrists to determine the presence or absence of Axis I psychiatric diagnoses using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)[36] in those 18 years and older, and the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL)[37] in those younger than 18 years. To qualify for the study, patients met DSM-IV diagnostic criteria for schizophrenia, bipolar disorder or major depressive disorder but did not meet the criteria for any other Axis I disorder. Healthy controls did not have a current or lifetime Axis I disorder or a history of psychotic, mood or other Axis I disorders in first-degree relatives, as determined by a detailed family history. Participants were excluded if any of the following were present: current or past substance or alcohol abuse or dependence, or a concomitant major medical disorder; any MRI contraindications; or a history of head trauma with loss of consciousness for 5 minutes or longer, or any neurologic disorder.

For all participants, we obtained symptom measures using the 17-item Hamilton Depression Rating Scale, the Hamilton Anxiety Rating Scale, the Young Mania Rating Scale and the Brief Psychiatric Rating Scale. We evaluated cognitive function (executive function) using the Wisconsin Card Sorting Test.

MRI acquisition

All participants underwent DTI. We acquired MRI data using a GE Signa HDx 3.0 T scanner with a standard 8-channel head coil at the First Affiliated Hospital of China Medical University. We acquired DTI using a single-shot spin echo planar imaging sequence with the following parameters: repetition time 17 000 ms, echo time 85.4 ms, image matrix = 120×120, field of view = 240×240 mm^2, 65 contiguous slices of 2 mm without a gap, 25 noncollinear directions (b = 1000 s/mm^2) together with an axial acquisition without diffusion weighting (b = 0), and voxel size 2.0 mm^3.

Data preprocessing

We processed DTI data using Pipeline for Analyzing braiN Diffusion imAges (PANDA; www.nitrc.org/projects/panda), a fully automated program for processing brain diffusion images. We used default program parameters to process the images. Steps were as follows: (1) converting Digital Imaging and Communications in Medicine (DICOM) files into Neuroimaging Informatics Technology Initiative (NIfTI) images, (2) brain extraction, (3) correction for eddy-current distortion and head motion, (4) correction for b-matrix, and (5) computation for diffusion tensor metrics. Next, we performed diagonalization to yield 3 pairs of eigenvalues and eigenvectors. We calculated an index corresponding to relative motion by averaging the displacement relative to the first time point. We observed no significant differences in mean relative head motion parameters between groups (major psychiatric disorders 0.49 ± 0.18 mm v. controls 0.47 ± 0.13 mm, $p = 0.07$). We also used head motion as a covariate in between-group analyses of FA values to explore the effect of head motion on DTI, and the results were consistent with our findings (Appendix 1, available at jpn.ca).

Based on the 3 eigenvalues, we computed FA on a voxel-by-voxel basis. Then, PANDA nonlinearly registered individual FA images of native space to the FMRIB58_FA template in Montreal Neurological Institute space with a customized spatial resolution ($2 \times 2 \times 2$ mm). The normalized FA was overlaid with image edges derived from the FA template, and then snapshot pictures were produced for quality control of FA normalization.[38] Ten participants (6 with schizophrenia, 1 with bipolar disorder, 2 with major depressive disorder and 1 healthy control) were excluded from subsequent analyses because of suboptimal imaging data quality (ghost, inadequate coverage of the brain or excessive head motion). Then, the FA images were smoothed with a 6 mm Gaussian kernel. We chose FA because it can reflect the connectivity of white matter, and a reduction in FA can reflect a decrease in myelination.[12] Furthermore, previous studies have shown that variations in the *NRG1* gene are associated with FA reduction in psychiatric disorders.[31–33]

Measurement of plasma NRG1-β1 levels

We obtained blood samples from 331 participants (141 healthy controls and 190 patients with major psychiatric disorders) between 1000 h and 1500 h. The 5 mL venous blood samples were collected and centrifuged at 2000 rpm for 10 minutes, and then the plasma was stored at −80°C for NRG1-β1 measurement. We made plasma NRG1-β1 determinations using the Human Premixed Multi-Analyte Kit (R&D Systems, Inc.) with the Human Magnetic Luminex Assay (Bio-Rad Laboratories, Inc.). Samples were magnetically labelled using a human magnetic premixed microparticle cocktail of antibodies (lot number L120614). After participants provided blood samples, they underwent MRI within 24 hours.

Statistical analysis

We combined findings for patients with schizophrenia, bipolar disorder and major depressive disorder into a "major psychiatric disorders" group and carried out analyses to compare that group with the healthy controls. We examined between-group effects on demographic and clinical characteristics, NRG1-β1 levels and cognitive measures using 2-sample *t* tests or χ^2 tests. Results were considered significant at $p < 0.05$.

First, we performed between-group analyses of FA values in SPM12 (a MATLAB toolbox, MATLAB version 9.1; www.fil.ion.ucl.ac.uk/spm/m), with diagnostic group as an independent factor and age and sex as covariates. To maintain a balance between type I and type II errors, we thought carefully about the issue of statistical thresholding and decided that the optimal, most balanced approach would be to report results at voxel-wise $p < 0.005$ with Gaussian random field (GRF) correction for cluster-level inference of $p < 0.05$. Other studies have used the same threshold.[39,40] We also performed exploratory analyses to investigate group differences in FA values with a stringent threshold (Appendix 1).

To further support the transdiagnostic approach, we performed analyses to compare the differences in plasma NRG1-β1 levels and FA maps among patients with schizophrenia, bipolar disorder and major depressive disorder.

Second, using the group difference FA map as a mask, we performed voxel-based correlation analyses within the major psychiatric disorders group to examine relationships between FA values in the regions showing common white matter alterations and NRG1-β1 levels, using age and sex as covariates. We used linear association for the correlation analyses, according to a linear correlation between NRG1 and the brain cortical tissue microarray from a previous study,[41] and a further general linear model was applied to the association between *NRG1* and white matter.[41,42] Statistical significance was set at a voxel-level inference of $p < 0.005$ with GRF correction for cluster-level inference of $p < 0.05$. For clusters with a significant correlation between FA values and NRG1-β1 levels in major psychiatric disorders, we extracted mean FA values for further analysis.

To further understand the clinical implications of NRG1-associated white matter abnormalities, we performed partial correlation analyses (2-tailed), controlling for age and sex, in the major psychiatric disorders group to explore the relationships between the mean FA values of NRG1-associated white matter abnormalities, clinical symptoms and executive function. Results were considered significant at $p < 0.05$, corrected for false discovery rate. Because the present sample had a wide age range (13–55 yr), we implemented 2-way analysis of variance with group (major psychiatric disorders or healthy controls) and age (≤ 30 yr or > 30 yr) as between-subjects factors, and sex as a covariate, to examine interactions between group and age. We also performed univariate analyses of variance to assess potential diagnosis × age interactions in extracted FA values and NRG1-β1.

We also performed analyses to explore differences in individual diagnostic groups (schizophrenia, bipolar disorder, major depressive disorder and healthy controls) in terms of

FA values, plasma NRG1-β1 levels, symptoms and alterations in cognitive function (Appendix 1).

Results

Demographic and clinical data

Detailed participant demographic and clinical data are outlined in Table 1.

We found no significant differences in terms of age, sex or smoking status between patients with major psychiatric disorders and healthy controls. As expected, we found significant differences in scores on the Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale, Young Mania Rating Scale and Wisconsin Card Sorting Test ($p < 0.001$, Table 1). We found no significant interaction between group and age in terms of FA values or NRG1-β1 levels. Demographic, clinical and cognitive characteristics for patients with schizophrenia, bipolar disorder and major depressive disorder are listed in Appendix 1, Table S1. Demographic characteristics for participants who had NRG1-β1 levels measured are listed in Appendix 1, Table S2.

White matter across diagnostic groups

Between-group analysis (major psychiatric disorders compared with healthy controls) showed that patients with major psychiatric disorders had significantly decreased FA values in several regions compared to healthy controls. These regions involved callosal, limbic–paralimbic–heteromodal, cortico-cortical and thalamocortical white matter, including the genu, body and splenium of the corpus callosum; the bilateral anterior and superior corona radiata; the bilateral posterior thalamic radiation; the bilateral anterior and posterior limb of the internal capsule; the bilateral external capsule; the bilateral superior longitudinal fasciculus; the cingulum; the bilateral inferior and superior fronto-occipital fasciculus; the bilateral cerebral peduncle; the fornix; the bilateral uncinate fasciculus; the right optic tract; the right mediodorsal thalamic nucleus; the left straight gyrus white matter; and the left olfactory radiation (Figure 1 and Appendix 1, Table S3).

Results showed common alterations of NRG1-β1 levels and FA in people with schizophrenia, bipolar disorder and major depressive disorder compared to healthy controls, suggesting a transdiagnostic continuum of major psychiatric disorders (Appendix 1, Figure S5).

NRG1-β1 levels across diagnostic groups

Compared to healthy controls, NRG1-β1 levels were significantly lower in patients with major psychiatric disorders ($p = 0.011$; Table 1).

Correlations between white matter alterations and NRG1-β1 levels

In the major psychiatric disorders group, 3 clusters showed a significant negative correlation between FA values and

Table 1: Participant demographics and clinical characteristics

Variable*	Healthy controls ($n = 318$)	Major psychiatric disorders ($n = 733$)	t/χ^2	p value
Demographics				
Age at scan, yr	28.59 ± 10.19	27.27 ± 10.24	1.93	0.054
Sex, M/F	131/187	267/466	2.14	0.14
Smoker, yes/no/unknown	27/132/159	66/251/416	0.99	0.32
Clinical characteristics				
First episode, yes/no/unknown	NA	475/202/56	—	—
Medication, yes/no/unknown	NA	484/247/2	—	—
Duration, mo	NA	33.79 ± 56.26	—	—
Hamilton Depression Rating Scale, total score	1.26 ± 2.29	13.16 ± 10.32	−28.006	< 0.001
Hamilton Anxiety Rating Scale, total score	1.32 ± 2.97	11.14 ± 10.15	−22.730	< 0.001
Young Mania Rating Scale, total score	0.31 ± 0.97	3.40 ± 6.85	−11.699	< 0.001
Brief Psychiatric Rating Scale, total score	18.51 ± 1.89	29.08 ± 9.91	−23.104	< 0.001
NRG1-β1†	9.92 ± 1.84	9.48 ± 1.97	6.659	0.011
Wisconsin Card Sorting Test (cognitive function)‡				
Correct responses	29.81 ± 12.04	24.00 ± 11.84	6.238	< 0.001
Categories completed	3.83 ± 2.17	2.82 ± 2.06	6.134	< 0.001
Total errors	18.25 ± 12.14	23.87 ± 11.87	−6.001	< 0.001
Perseverative errors	6.54 ± 6.96	9.58 ± 9.16	−4.998	< 0.001
Nonperseverative errors	11.59 ± 6.98	14.34 ± 7.40	−4.825	< 0.001

F = female; M = male; NA = not applicable; NRG1 = neuregulin 1.
*Data are presented as mean ± standard deviation unless otherwise specified.
†Healthy controls, $n = 141$; major psychiatric disorders, $n = 190$.
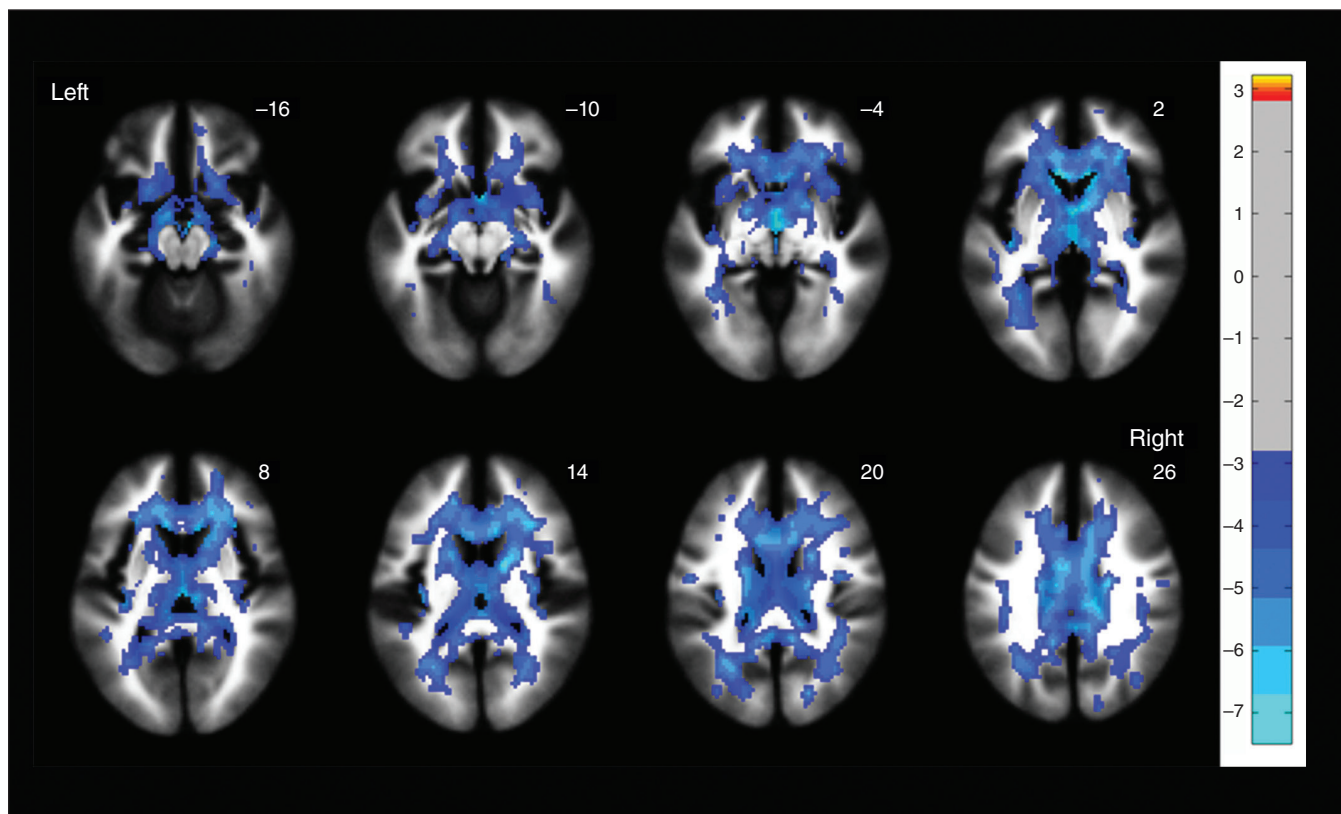‡Healthy controls, $n = 249$; major psychiatric disorders, $n = 470$.

Figure 1: Significant differences in fractional anisotropy values between patients with major psychiatric disorders and healthy controls. Significance was set at $p < 0.005$ at the voxel level, with Gaussian random field correction for cluster-level inference of $p < 0.05$.

NRG1-β1 levels. These clusters consisted of callosal, limbic–paralimbic–heteromodal, corticocortical and thalamocortical white matter regions: white matter A included the genu of the corpus callosum, the right external capsule, the right uncinate fasciculus and the right inferior fronto-occipital fasciculus; white matter B included the fornix and the right optic tract; and white matter C included the left right inferior fronto-occipital fasciculus, the left straight gyrus white matter and the left olfactory radiation (Figure 2 and Table 2).

Correlations between white matter alterations and clinical variables

In the major psychiatric disorders group, the somatic anxiety factor scores and the total score on the Hamilton Depression Rating Scale were positively correlated with FA values in all clusters that showed negative correlations with NRG1-β1 (Table 3). Total score on the Hamilton Anxiety Rating Scale and categories completed on the Wisconsin Card Sorting Test were positively correlated with FA values in the white matter B cluster. We found no significant correlations between FA values in clusters that showed a negative correlation with NRG1-β1 levels and the psychic anxiety, core depressive and anorexia factor scores on the Hamilton Depression Rating Scale, the Young Mania Rating Scale, the Brief Psychiatric Rating Scale or other scores on the Wisconsin Card Sorting Test.

Individual patient groups (schizophrenia, bipolar disorder or major depressive disorder) showed analogous white matter alterations, NRG1-β1 levels and clinical manifestations (Appendix 1, Figures S1 to S5).

Discussion

This was the first study to use a transdiagnostic approach to identify abnormal white matter related to NRG1-β1 levels and clinical and cognitive symptoms in major psychiatric disorders. We found widespread alterations in FA and decreased plasma NRG1-β1 levels in the major psychiatric disorders group relative to healthy controls. Further analysis showed that FA values were related to NRG1-β1 levels in the major psychiatric disorders group, predominantly in callosal, limbic–paralimbic–heteromodal, corticocortical and thalamocortical white matter. Moreover, these NRG1-associated white matter abnormalities were related to depressive and anxiety symptoms and to executive function in the major psychiatric disorders group. We observed analogous alterations across the 3 disorders (schizophrenia, bipolar disorder and major depressive disorder) in terms of white matter alterations, NRG1-β1 levels and clinical manifestations. These results add to an increasing body of literature implicating NRG1 in the mechanisms that underlie white matter abnormalities in psychiatric disorders and extend this literature by exploring the clinical implications of NRG1-associated white matter abnormalities.
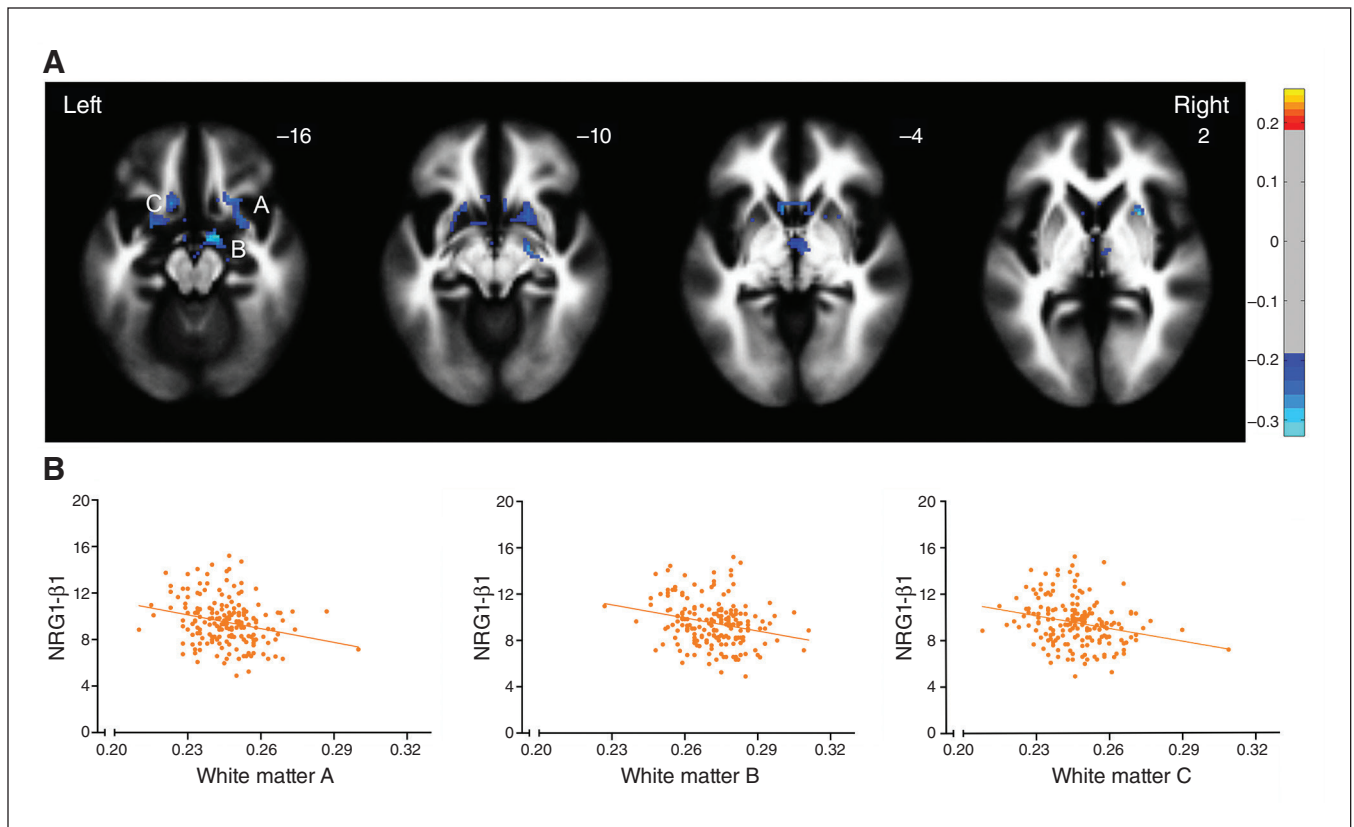
Figure 2: Patients with major psychiatric disorders showed significant correlations between fractional anisotropy in white matter and NRG1-β1. (A) Regions that showed significant associations with NRG1-β1 in patients with major psychiatric disorders. Significance was set at $p < 0.005$ at the voxel level, with Gaussian random field correction for cluster-level inference of $p < 0.05$. (B) Scatter plots of the association between fractional anisotropy and NRG1-β1 in patients with major psychiatric disorders. White matter A = genu of corpus callosum, right external capsule, right uncinate fasciculus, right inferior fronto-occipital fasciculus; white matter B = fornix, right optic tract; white matter C = left inferior fronto-occipital fasciculus, left straight gyrus white matter, left olfactory radiation.

Table 2: Patients with major psychiatric disorders who showed significant correlations between fractional anisotropy in white matter and NRG1-β1*

Index	White matter label	Cluster size, voxels	MNI coordinates, x, y, z	R
White matter A	Genu of corpus callosum, right external capsule, right uncinate fasciculus, right inferior fronto-occipital fasciculus	283	26, 12, 4	−0.312
White matter B	Fornix, right optic tract	183	14, −2, 16	−0.307
White matter C	Left inferior fronto-occipital fasciculus, left straight gyrus white matter, left olfactory radiation	161	−14, 18, −18	−0.269

MNI = Montreal Neurological Institute; NRG1 = neuregulin 1.
*Significance was set at $p < 0.005$ at the voxel level, with Gaussian random field correction for cluster-level inference of $p < 0.05$.

Associations between white matter alterations and NRG1-β1 levels in major psychiatric disorders

In this study, FA values[14,43] and plasma NRG1-β1 levels were decreased in the major psychiatric disorders group relative to healthy controls, consistent with the literature.[44,45] In psychiatric disorders, NRG1 could have an effect on white matter alterations. Previous studies have demonstrated that NRG1–ErbB signalling is associated with white matter at multiple levels in psychiatric disorders, from genetic variations to gene expression. Genetic imaging studies have found that variations in *NRG1* are associated with white matter in the right uncinate fasciculus, corpus callosum, external capsule and inferior fronto-occipital fasciculus;[35,42] the other NRG1-associated white matter alterations reported in the present study have not been previously detected. Studies have also shown that the expression levels or function of NRG1 and ErbB are altered in major psychiatric disorders.[46,47] Translational research suggests a causal role, because animal studies have found that decreased ErbB expression in white matter

Table 3: Partial correlations between alterations in white matter integrity and clinical variables in patients with major psychiatric disorders

Clinical variable	White matter A		White matter B		White matter C	
	r	p value	r	p value	r	p value
Hamilton Depression Rating Scale						
Somatic anxiety (factor) score	0.109	0.005*	0.127	0.001*	0.102	0.009*
Psychic anxiety (factor) score	0.066	0.10	0.04	0.31	0.078	0.048†
Core depressive (factor) score	0.059	0.13	0.053	0.17	0.073	0.06
Anorexia (factor) score	0.063	0.11	0.074	0.06	0.065	0.10
Total score	0.098	0.013*	0.097	0.013*	0.105	0.007*
Hamilton Anxiety Rating Scale, total score	0.09	0.027†	0.1	0.013*	0.078	0.054
Young Mania Rating Scale, total score	−0.038	0.35	−0.047	0.25	0.019	0.63
Brief Psychiatric Rating Scale						
Anxiety and depression (factor), score	0.07	0.10	0.065	0.13	0.046	0.29
Lack of energy (factor), score	−0.025	0.56	−0.094	0.028†	−0.068	0.11
Thought disorder (factor), score	−0.003	0.95	−0.078	0.07	−0.007	0.88
Activity (factor), score	0.004	0.92	−0.043	0.32	0.029	0.50
Hostility (factor), score	−0.003	0.95	−0.058	0.18	−0.002	0.97
Total score	0.019	0.66	−0.051	0.23	−0.001	0.99
Wisconsin Card Sorting Test						
Corrected responses	0.074	0.11	0.064	0.16	0.071	0.12
Categories completed	0.114	0.014†	0.123	0.008*	0.11	0.017†
Total errors	−0.061	0.19	−0.062	0.18	−0.066	0.16
Perseverative errors	−0.001	0.98	−0.017	0.71	−0.009	0.85
Nonperseverative errors	−0.105	0.023†	−0.073	0.12	−0.103	0.026†

FDR = false discovery rate; white matter A = genu of corpus callosum, right external capsule, right uncinate fasciculus, right inferior fronto-occipital fasciculus; white matter B = fornix, right optic tract; white matter C = left inferior fronto-occipital fasciculus, left straight gyrus white matter, left olfactory radiation.
*Significant at $p_{FDR} < 0.05$.
†Significant at $p < 0.05$ (uncorrected).

tracts, including the corpus callosum, could cause white matter alterations in major psychiatric disorders.[48]

It is possible that white matter alterations are influenced by NRG1 regulation of oligodendrocyte and myelination. Defects in NRG1–ErbB signalling could result in alterations of oligodendrocyte development and abnormal myelination, resulting in alterations of white matter.[46,48] The potential pathophysiological role of NRG1 in psychiatric disorders might be to alter connections between the prefrontal cortex and other brain regions[31] such as the genu of the corpus callosum, the uncinate fasciculus, the inferior fronto-occipital fasciculus and the external capsule. Several groups have assessed gene and protein expression of NRG1 and ErbB in postmortem brains and found dysregulations primarily in the prefrontal cortex in people with psychiatric disorders.[28,49,50] There is also immunohistochemical evidence for impaired NRG1 signalling in the prefrontal cortex in people with psychiatric disorders.[51] In addition, negative correlations between FA values and plasma NRG1-β1 levels found in the major psychiatric disorders group in the present study might suggest compensatory effects under pathological conditions, playing an important role in brain plasticity.[29,52] The negative correlation could be attributed to remyelination after white matter damage. As one of the few spontaneous repair processes in the central nervous system, remyelination can provide a certain degree of myelin reconstitution, but it remains insufficient for the deficit.[53] White matter microstructure appears altered in major psychiatric disorders and may reflect decreased

myelination compared to healthy controls. The relative lack of myelination may drive compensatory responses in people with major psychiatric disorders, resulting in the negative correlation between FA and expression levels of the myelination-related gene NRG1.[54]

Associations between NRG1-associated white matter alterations, clinical symptoms and cognition in people with major psychiatric disorders

In the present study, NRG1-associated white matter alterations were also associated with Wisconsin Card Sorting Test scores in patients with major psychiatric disorders. Previous studies have suggested a strong association between white matter alterations and cognition.[55] In our study, executive function was correlated with FA values in the fornix and right optic tract in the major psychiatric disorders group. The fornix is part of the limbic system, and as the primary efferent network from the hippocampus, it is critical for cognitive function.[56] Nestor and colleagues[57] have reported reduced executive functioning correlated with fornix alteration in people with schizophrenia.

These NRG1-associated white matter abnormalities were also related to depressive and anxiety symptoms in our study. Reports have indicated that these NRG1-associated white matter abnormalities may be involved in emotion processing.[58–60] The corpus callosum is critical to interhemispheric communication and to the integration of emotional

information.[58,59] Together, the uncinate fasciculus and inferior fronto-occipital fasciculus form the ventral external capsule, and these and the olfactory radiation contain pathways that extend into limbic brain regions that are important for emotional regulation.[60,61] Interestingly, we observed that NRG1-associated white matter abnormalities were positively correlated with scores on the Hamilton Depression Rating Scale and the Hamilton Anxiety Rating Scale. The positive correlations we found might reflect the relationship between NRG1-associated white matter abnormalities and clinical symptoms (of depression and anxiety) under pathological conditions. Altered NRG1-associated white matter, which is more likely to be a patient trait-related change,[62,63] might contribute to alterations in functional connectivity between prefrontal and limbic brain regions,[64,65] and subsequently to dysfunction of emotional processing.[66] However, FA differences may simply reflect changes in orientation-dependent aspects of white matter microstructure, because FA is not a direct measure of white matter integrity. Further interpretation of FA findings in relation to white matter integrity warrants further study.[13]

Limitations

This study had several limitations. First, most patients with a major psychiatric disorder were taking psychotropic medications at the time of the study, which may have altered white matter and NRG1-β1 levels. However, previous studies have shown limited evidence for the effect of medications on white matter[67] and NRG1-β1.[68] Further studies in medication-naive patients are needed to clarify these issues. Second, our sample had a relatively wide age range (13–55 yr), and the effects of age on white matter development may have confounded our findings. We performed an analysis to test for interactions between group and age and found no significant interaction between group and age on FA values and NRG1-β1 levels. Regions that showed group × age interactions did not overlap with the regions in which NRG1-associated white matter abnormalities were located. Furthermore, we found no significant differences in age between the major psychiatric disorders group and the healthy controls. We also found no significant correlations between age and NRG1-associated white matter abnormalities in the major psychiatric disorders group. Further studies of white matter development could be performed to clarify the effects of age. Third, this study was cross-sectional, and we have limited details related to the longitudinal course and severity of symptoms. Clearly, longitudinal research is needed to better understand the relationships between white matter, NRG1-β1 and clinical symptoms in psychiatric disorders. Fourth, it is not entirely clear to what extent plasma NRG1 levels reflect levels in the brain. However, even if NRG1 abnormalities in the blood were not a perfect mirror of pathological processes in brain, they could represent distinct molecular changes that are specific to the primary pathophysiology.[69] As technology advances, in vivo levels of NRG1 in cerebrospinal fluid could be measured to verify results. In addition, smoking might be associated with NRG1-β1 levels.[26] The effect of smoking on NRG1-β1 in this study was unclear because of a lack of information on the association between the smoking status of patients with major psychiatric disorders and NRG1-β1 data. There also might be complex associations between NRG1 and FA. Further studies are needed to clarify this issue.

Conclusion

This study used a dimensional approach to identify transdiagnostic white matter alterations that might represent important common neuroimaging substrates and indicate markers for potential biological mechanisms of major psychiatric disorders. The NRG1-associated white matter abnormalities found in our study could also be associated with depressive and/or anxiety symptoms and with executive function, and may represent a treatment target for psychiatry disorders.

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