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Original Article

Abnormal frontal white matter tracts in bipolar disorder: a diffusion tensor imaging study

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Objectives: Prefrontal white matter has been hypothesized to be integral to the pathophysiology of bipolar disorder. Recent morphometric studies however, have not observed changes in white matter in bipolar patients. We hypothesized that changes in prefrontal function in bipolar disorder, widely reported in the literature, may be related to a loss of white matter tract integrity with a resultant dysconnectivity syndrome. In this study we utilized diffusion tensor imaging (DTI) to examine prefrontal white matter in patients with bipolar disorder.

Methods: Nine patients with bipolar disorder and nine healthy controls were recruited. DTI and localizing anatomic data were acquired, and regions of interest (ROIs) identified in the prefrontal white matter at 15, 20, 25, and 30 mm superior to the anterior commissure (AC). Fractional anisotropy (FA) and trace apparent diffusion coefficient (TADC) were compared by ROI between study groups.

Results: The FA of ROIs 25 and 30 mm above the AC was significantly reduced in patients with bipolar disorder; FA of all ROIs showed high-medium to large effect sizes. No significant group differences were identified in TADC.

Conclusions: Our findings suggest that a loss of bundle coherence is present in prefrontal white matter. This loss of coherence may contribute to prefrontal cortical pathology in patients with bipolar disorder.

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Several lines of evidence, including morphometric and functional imaging studies, suggest the presence of prefrontal cortical dysfunction in patients with bipolar disorder (1). Changes in prefrontal cortical activation and the associated cognitive deficits observed in bipolar disorder have been hypothesized to represent elements of a dysfunctional network linking prefrontal regions with other subcortical and cortical structures. This hypothesis has been buttressed by a study from Ketter and colleagues showing linkage between decreased glucose metabolism in the prefrontal cortex of depressed patients with bipolar disorder and increased subcortical metabolism (2). One element of this putative network dysfunction has been suggested to be a dysconnectivity syndrome involving white matter pathways connecting structures functionally and anatomically linked to the prefrontal cortex, similar to that suggested to be involved in schizophrenia (3– 5).

Evidence of neuropathology in white matter tracts serving the prefrontal cortex however, has been mixed. Increased numbers of white matter hyperintensities (WMH) have been widely observed in patients with bipolar disorder, a phenomenon suggested to be linked to white

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matter pathology (6– 9). Furthermore, patients with bipolar mania were found by Strakowski et al to have decreased whole brain white matter volume compared with healthy controls, and Dewan et al. noted increased white matter density in patients with bipolar disorder on computerized tomography (10, 11). A recent study however, using more sophisticated measurement techniques failed to identify differences in white matter neuronal density or distribution in patients with bipolar disorder (12). A more specific examination of prefrontal white matter also failed to demonstrate significant differences between patients with bipolar disorder and healthy controls (13). Similarly, no significant change in T1 proton relaxation times, a measurement of white matter integrity, was observed in the frontal cortex of patients with bipolar disorder (14). The lack of consistent findings with gross measures of prefrontal white matter suggests that neuropathologic changes may represent a more subtle loss of organizational structure.

Diffusion tensor imaging (DTI) provides a means for studying axonal structure and coherence by measuring the *in vivo* movement of water molecules in the human brain. Brownian motion of water molecules results in diffusion throughout the local environment. The degree of diffusion may be affected by several factors including molecular weight, environmental viscosity and ambient temperature, and may be quantified by the diffusion coefficient (15). In neuronal white matter, microanatomic features including internal structural features of the axon, the myelin sheath, and the tightly packed nature of the axonal bundle restrict water diffusion. These constraints result in a trace apparent diffusion coefficient (TADC) that is partially dependent on elements of white matter composition. Increased TADC may be related to any factor that removes some of the impediments to free diffusion in the white matter tract. Changes in white matter TADC have been observed with axonal demyelination, axonal loss, and edema (15).

In addition to the TADC, the structure of the axonal bundle may be studied using a complementary measure that represents the degree of anisotropy of water diffusion. The volume over which a water molecule diffuses without constraint forms a sphere. The structure of normal white matter limits diffusion in some directions and results in preferential diffusion in others. This disparity in barriers to diffusion parallel and perpendicular to the axonal bundle gives rise to a loss of sphericity, often reported as the fractional anisotropy (FA) (15). While increased TADC is more likely to represent a loss of barriers to diffusion, decreased FA may occur with a loss of bundle coherence, a disruption in the organization of white matter tracts, alone (16). The use of DTI to study white matter integrity in patients with affective disorders has been extremely limited. A single study in elderly depressed patients however, found that a lower frontal FA inversely correlated with response to antidepressant treatment (17). In this study we hypothesized that patients with bipolar disorder would demonstrate changes in measures of diffusion consistent with a loss of white matter axonal bundle integrity.

Methods

Participants

Nine patients (four men, five women) with bipolar I disorder were recruited from ongoing outcome studies and nine healthy subjects (six men, three women) were recruited in response to local advertisement or by word of mouth. Subjects with bipolar disorder were diagnosed by Structured Clinical Interview for DSM-IV (SCID) (18) by a board certified psychiatrist and were free of concurrent psychiatric or medical illness, including substance use disorders. Bipolar patients were receiving standard pharmacotherapy including lithium, divalproex, and antipsychotics. Healthy subjects had no Axis I psychiatric conditions, including substance dependence, as determined by SCID by a board certified psychiatrist or PhD level psychologist. Healthy subjects reported no history of Axis I psychiatric conditions in any first-degree relatives. No healthy subjects were receiving medication at the time of the study. All subjects were right handed on the Crovitz Handedness Inventory (19).

Bipolar subjects had a mean age of 32 $\pm$ 8 years and an education of 16 $\pm$ 3 years; healthy subjects had a mean age of 31 $\pm$ 7 years and an education of 15 $\pm$ 2 years. There was no significant difference in age ($t = 0.81$, df = 16, $p = 0.24$) or education ($t = 0.36$, df = 16, $p = 0.72$) between the two groups. All subjects were in good health. All subjects demonstrated facility with English and a clear understanding of the procedures, risks and intent of the study. All subjects provided written informed consent, which was obtained after study procedures had been explained in detail, prior to their participating in the study.

Imaging

Scans were performed with a 3.0 Tesla Bruker Biospec scanner (Bruker Biospin GmbH, Ettlingen, Germany) equipped with a head gradient

insert. The gradient eddy currents were minimized using an automated pre-emphasis adjustment routine (20). Following a 3-plane gradient echo scan for alignment and localization, a shim procedure was performed to generate a homogenous, constant magnetic field. Diffusion-weighted spin-echo single-shot echo-planar magnetic resonance (MR) imaging was performed with the following parameters: repetition time ms/echo time ms, 6000/87; matrix, 64×128; field of view, 19.2×25.6 cm; section thickness, 5 mm; readout bandwidth, 125 kHz; Δ, 40 ms; δ, 18 ms. Twenty-four sections centered around the corpus callosum were acquired. Twenty-five gradient directions, determined via an electrostatic repulsive model (21), were used with a gradient strength of 30 mT/m, for a b value (diffusion-weighting factor) of 710 s/mm^2. Three additional images were acquired with no diffusion weighting ($b = 0$ s/mm^2). The total imaging time for the entire diffusion-tensor MR imaging sequence was approximately 3 min. In addition, a fluid-attenuated inversion recovery-echo planar imaging (FLAIR-EPI) scan with the same parameters and no diffusion weighting, and a high-resolution T1-weighted 3-D brain scan using a modified driven equilibrium Fourier transform (MDEFT) protocol (TI = 550 ms, TR = 16.5 ms, TE = 4.3 ms, FOV = $25.6 \times 19.2 \times 14.4$, $256 \times 128 \times 96$, flip angle = 20 °) to provide anatomical localization were also obtained (22).

Image processing and analysis

Image data were processed using the Children's Hospital Imaging Processing Software (CHIPS®), based on the IDL software environment (Research Systems, Boulder, CO, USA), and developed by the Imaging Research Center at Children's Hospital Research Foundation. Geometric distortion because of residual eddy currents in the diffusion-weighted echo-planar MR images was corrected with an iterative Levenberg-Marquardt least squares algorithm. As the presence of cerebrospinal fluid in the image with no diffusion weighting ($b = 0$ s/mm^2) could lead to excessive stretching in the diffusion-weighted MR images, the FLAIR-EPI scans were used as a reference to find the optimum values of shear, stretch, and shift (23). The distortion as a result of the static magnetic field inhomogeneities was corrected using the multiecho reference method (24, 25). By using a k-mean clustering algorithm, a white matter template was applied to exclude cortical gray matter and cerebrospinal fluid (26). The echo-planar images were then transformed into Talairach space. To increase the signal-to-noise ratio, the images were filtered by using a Gaussian kernel with a full width at half maximum of 3 mm prior to the transformation. For each data set, the diffusion tensor matrix eigenvectors, eigenvalues, trace ADC, and FA were calculated. TADC and FA are rotationally invariant (i.e. independent of the actual fiber direction) (27).

Regions of interest (ROIs) were chosen *a priori* to include white matter tracts contiguous with areas previously observed in our functional imaging studies to demonstrate disparate activation in patients with bipolar disorder (28). Regions chosen encompassed 5 voxels in diameter and were placed 15, 20, 25 and 30 mm above the anterior commissure (AC) (Fig. 1). Placement was patterned after that of Lim and others (5, 29). All ROIs were drawn on the high-resolution T1-weighted anatomic scan. ROIs were drawn by a single investigator (CA) and applied to the spatially normalized data to minimize intersubject variation. Individual scans were inspected to ensure consistency of placement. Mean TADC and FA were determined for individual ROIs (left and right combined).

The TADC and FA were separately compared across subject groups by ROI and by the sum of combined ROIs, each analyzed separately using a univariate analysis of variance (ANOVA). Age and education were included as covariates to control for between group demographic differences. All statistics were two-tailed.

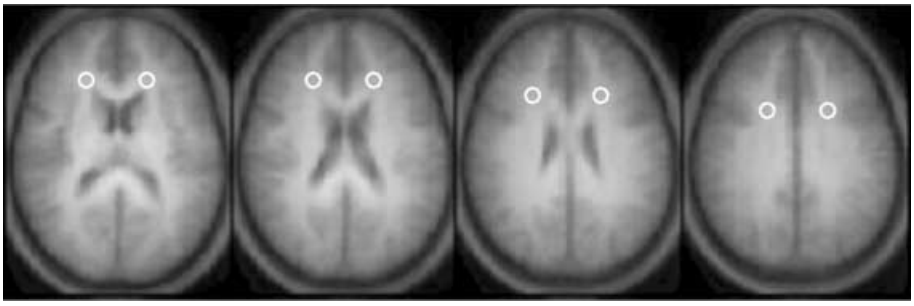

Fig. 1. Axial slices with ROI placement at 15, 20, 25, and 30 mm above the anterior commissure.

Results

Fractional anisotropy and TADC data for patients with bipolar disorder and healthy controls are presented in Tables 1 and 2. The FA of the ROIs placed 25 and 30 mm above the AC was significantly reduced in patients with bipolar disorder even after covarying for age and education. All ROIs, and the ROIs combined, showed high-medium to large effect sizes (Table 1).

No ROIs showed significant between group differences in TADC, after controlling for age and education. Between group comparisons of TADC showed only small to low-medium effect sizes (Table 2).

Total brain size was compared between patients with bipolar disorder and healthy controls. No significant differences were identified ($t = 1.21$, $df = 16$, $p = 0.24$).

Discussion

This is the first study to identify differences in anisotropy between patients with bipolar disorder and healthy controls. Patients with bipolar disorder showed decreased FA in peripheral white matter tracts linking the prefrontal cortex with subcortical and other cortical regions. More superior areas of white matter, near upper portions of Brodman area 10 and the lower portions of Brodman area 9, were particularly affected. ROIs more adjacent to fronto-polar prefrontal cortex showed smaller increases in FA, suggesting that changes in white matter anisotropy are not indiscriminate and may conform to areas involved in cognitive functions previously observed to be affected by bipolar disorder. Reduced white matter FA may be related to axonal pathology or demyelination, or may represent a loss of axonal bundle coherence, any of which may result in a loss of anisotropy. Patients with bipolar disorder did not however, demonstrate a significant increase in TADC. The TADC would be expected to be affected by a loss of cellular integrity or destruction of myelin sheath. A loss of bundle coherence however, would not impact the local diffusion rate and would therefore not result in an increase in TADC.

Table 1. White matter fractional anisotropy by group

Region of interest	Bipolar patients (±S.D.) (n = 9)	Healthy controls (±S.D.) (n = 9)	Comparison (controlling for age and education)*	Effect size (*d*)
15 mm above AC	0.2200 ± 0.0439	0.2477 ± 0.0372	$F = 1.76$ $p = 0.21$	0.6840
20 mm above AC	0.1962 ± 0.0363	0.2250 ± 0.0348	$F = 2.89$ $p = 0.11$	0.8113
25 mm above AC	0.1817 ± 0.0277	0.2155 ± 0.0371	$F = 5.39$ $p = 0.04$	1.0426
30 mm above AC	0.1849 ± 0.0224	0.2172 ± 0.0274	$F = 8.78$ $p = 0.01$	1.2947
Total ROI	0.7827 ± 0.1233	0.9054 ± 0.1248	$F = 4.41$ $p = 0.05$	0.9883

*No correction was carried out for the number of comparisons.

Table 2. Trace apparent diffusion coefficient by group

Region of interest	Bipolar patients (±S.D.) (n = 9)	Healthy controls (±S.D.) (n = 9)	Comparison (controlling for age and education)*	Effect size (*d*)
15 mm above AC	7.82E-06 ± 1.06E-06	7.97E-06 ± 6.39E-07	$F = 0.18$ $p = 0.68$	0.1649
20 mm above AC	7.81E-06 ± 1.41E-06	7.77E-06 ± 3.85E-07	$F = 0.00$ $p = 0.99$	0.0521
25 mm above AC	8.50E-06 ± 1.54E-06	8.07E-06 ± 4.45E-07	$F = 0.49$ $p = 0.50$	0.4316
30 mm above AC	8.26E-06 ± 1.15E-06	7.89E-06 ± 4.38E-07	$F = 0.66$ $p = 0.43$	0.4763
Total ROI	3.24E-05 ± 5.04E-06	3.17E-05 ± 1.61E-06	$F = 0.12$ $p = 0.74$	0.2146

*No correction was done for the number of comparisons.

Differences in FA alone suggest that bipolar disorder is associated with a loss of bundle coherence in prefrontal peripheral white matter tracts. We and others have previously observed deficits in cognitive domains associated with prefrontal cortex, in patients with bipolar disorder (30– 34). Functional imaging studies in patients with bipolar disorder have been consistent with these findings; patients with bipolar disorder showed increased prefrontal activation during both attention and working memory tasks (1). Based on evidence of cognitive deficits in bipolar disorder, this increased activation has been interpreted to be related to cognitive inefficiency, as has been described in patients with schizophrenia (35). The neuropathologic origin of these cognitive deficits, either in local pathology or within larger cognitive networks encompassing the prefrontal cortex has not been clear. These DTI findings suggest that at least a portion of the cognitive deficits observed in bipolar disorder may be related to a disruption in network connectivity.

Several studies have suggested that repeated affective episodes may lead to neuronal pathology in patients with bipolar disorder with concomitant decrements in some cognitive abilities. The absence of evidence suggesting axonal destruction in the TADC findings however, suggests that bipolar disorder may also be associated with a loss of white matter bundling. While disorganization of white matter tracts may be a neuropathic phenomenon, a loss of bundle coherence may be developmental in origin. White matter formation and development begins during the prenatal period and extends through early adulthood, suggesting the presence of neuropathologic changes prior to the onset of affective symptomatology marking the overt appearance of bipolar disorder.

Limitations to this study arise from the relatively small sample size. These results need to be considered to be preliminary pending replication in a larger study. Moreover, because of the limited number of subjects, we confined ourselves to studying a region of white matter that based on our functional imaging studies, we hypothesized to be likely to show evidence of white matter pathology. With a larger subject population, we would extend our analysis to include other, more exploratory brain regions. The FA of two of the ROIs studied failed to show significant differences between subject groups, probably due in part to the small number of subjects involved. We have attempted to compensate to some degree by including effect size calculations in our analysis. The large effect sizes of the two non-significantly affected ROIs suggest that in a study with a larger number of participants, these measures would also likely be found to be significantly reduced in patients with bipolar disorder. The limited sample size also impacts interpretation of our TADC findings. TADC potentially lacks sufficient sensitivity to identify subtle loss of axonal integrity, particularly in a small subject sample.

All bipolar subjects were receiving medications at the time of this study. A neurotoxic effect on white matter tracts could lead to our finding differences in FA. Such a neurotoxic effect however would be likely to increase ADC as well. Moreover, while the majority of DTI studies in patients with schizophrenia failed to address medication status, the studies that did so concluded that medications did not have a significant effect on their findings (3, 4, 36, 37). We did not specifically screen subjects for WMH. While these may be evidence of white matter pathology, we felt that excluding bipolar patients with WMH might skew our subject population by including only those patients with the least white matter changes. The anisotropic nature of the voxels in this study is also of note. As a result, partial volume effects may vary to some degree, depending on fiber orientation.

There are small demographic differences between bipolar and control participants. While several previous studies have examined gender effects on DTI and failed to find a correlation (36, 38, 39), several studies have noted age related increases in measures of diffusion. No such effects of education have been reported; education however, has previously been reported to have a possible neuroprotective effect (40, 41). Although differences in age and education were not significant, we controlled for both of these variables in our analysis.

Our findings extend previous functional imaging studies by providing support for suggestions that a loss of network connectivity may be at least one of the mechanisms involved in the symptomatology of bipolar disorder. While the limitations imposed by the small sample size are clear and findings should be considered preliminary, this study demonstrates evidence of white matter pathology in peripheral prefrontal white matter tracts of patients with bipolar disorder.

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References

1. Strakowski SM, DelBello M, Adler CM, Cecil KM, Sax KW. Neuroimaging in bipolar disorder. Bipolar Disord 2000; 2: 148–164.

2. Ketter TA, Kimbrell TA, George MS et al. Effects of mood and subtype on cerebral glucose metabolism in treatment-resistant bipolar disorder. Biol Psychiatry 2001; 49: 97–109.
3. Buchsbaum MS, Tang CY, Peled S et al. MRI white matter diffusion anisotropy and PET metabolic rate in schizophrenia. Neuroreport 1998; 9: 425–430.
4. Lim KO, Hedehus M, Moseley M, Crespigny A, Sullivan EV, Pfefferbaum A. Compromised white matter tract integrity in schizophrenia inferred from diffusion tensor imaging. Arch Gen Psychiatry 1999; 56: 367–374.
5. Hoptman MJ, Volavka J, Johnson G, Weiss E, Bilder RM, Lim KO. Frontal white matter microstructure, aggression, and impulsivity in men with schizophrenia: a preliminary study. Biol Psychiatry 2002; 52: 9–14.
6. Dupont RM, Jernigan TL, Gillin JC, Butters N, Delis DC, Hesselink JR. Subcortical signal hyperintensities in bipolar patients detected by MRI. Psychiatry Res 1987; 21: 357–358.
7. Dupont RM, Jernigan TL, Butters N et al. Subcortical abnormalities detected in bipolar affective disorder using magnetic resonance imaging. Clinical and neuropsychological significance. Arch Gen Psychiatry 1990; 47: 55–59.
8. Figiel GS, Krishnan KR, Rao VP et al. Subcortical hyperintensities on brain magnetic resonance imaging: a comparison of normal and bipolar subjects. J Neuropsychiatry Clin Neurosci 1991; 3: 18–22.
9. Swayze VW, Andreasen NC, Alliger RJ, Ehrhardt JC, Yuh WT. Structural brain abnormalities in bipolar affective disorder. Ventricular enlargement and focal signal hyperintensities. Arch Gen Psychiatry 1990; 47: 1054–1059.
10. Strakowski SM, Wilson DR, Tohen M, Woods BT, Douglass AW, Stoll AL. Structural brain abnormalities in first–episode mania. Biol Psychiatry 1993; 33: 602–609.
11. Dewan MJ, Haldipur CV, Lane EE, Ispahani A, Boucher MF, Major LF. Bipolar affective disorder. I. Comprehensive quantitative computed tomography. Acta Psychiatr Scand 1988; 77: 670–676.
12. Beasley CL, Cotter DR, Everall IP. Density and distribution of white matter neurons in schizophrenia, bipolar disorder and major depressive disorder: no evidence for abnormalities of neuronal migration. Mol Psychiatry 2002; 7: 564–570.
13. Lopez-Larson MP, DelBello MP, Zimmerman ME, Schwiers ML, Strakowski SM. Regional prefrontal gray matter and white matter abnormalities in bipolar disorder. Biol Psychiatry 2002; 52: 93–100.
14. Dolan RJ, Poynton AM, Bridges PK, Trimble MR. Altered magnetic resonance white-matter T1 values in patients with affective disorders. Br J Psychiatry 1990; 157: 107–110.
15. Beaulieu C. The basis of anisotropic diffusion in the nervous system–a technical review. NMR Biomed 2002; 15: 435–455.
16. Foong J, Symms MR, Barker GJ, Maier M, Miller DH, Ron MA. Investigating regional white matter in schizophrenia using diffusion tensor imaging. Neuroreport 2002; 13: 333–336.
17. Alexopoulos GS, Kiosses DN, Choi SJ, Murphy CF, Lim KO. Frontal white matter microstructure and treatment response of late-life depression: a preliminary study. Am J Psychiatry 2002; 159: 1929–1932.
18. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV Axis I Disorders – Patient Edition (SCID-I/P, Version 2.0, 4/97 revision). New York: Biometrics Research Department, New York State Psychiatric Institute, 1997.
19. Crovitz HF, Zener K. A group test for assessing hand- and eye-dominance. Am J Psychol 1962; 75: 271–276.
20. Schmithorst VJ, Dardzinski BJ. Automatic gradient preemphasis adjustment: A 15-minute journey to improved diffusion-weighted echo planar imaging. Magn Reson Med 2002; 47: 208–212.
21. Jones DK, Horsfield MA, Simmons A. Optimal strategies for measuring diffusion in anisotropic systems by magnetic resonance imaging. Magn Reson Med 1999; 42: 515–525.
22. Ugurbil K, Garwood M, Ellermann J et al. Imaging at high magnetic fields: initial experience at 4T. Magn Reson Quart 1993; 9: 259–277.
23. de Crespigny A, Moseley M. Eddy current induced image warping in diffusion weighted EPI. Proc. ISMRM 6th Annual Meeting 1998; p. 661.
24. Chen NK, Wyrwicz AM. Correction for EPI distortions using multi-echo gradient-echo imaging. Magn Reson Med 1999; 41: 1206–1213.
25. Schmithorst VJ, Dardzinski BJ, Holland SK. Simultaneous correction of ghost and geometric distortion artifacts in EPI using a multiecho reference scan. IEEE Trans Med Imaging 2001; 20: 535–539.
26. Neil JJ, Shiran SI, McKinstry RC et al. Normal brain in human newborns: apparent diffusion coefficient and diffusion anisotropy measured by using diffusion tensor MR imaging. Radiology 1998; 209: 57–66.
27. Baratti C, Barnett AS, Pierpaoli C. Comparative MR imaging study of brain maturation in kittens with T1, T2, and the trace of the diffusion tensor. Radiology 1999; 210: 133–142.
28. Adler CM, Strakowski SM, Holland SK, Schmithorst V, Enseleit S. An fMRI study of working memory in bipolar disorder. Presented at the Society of Biological Psychiatry, New Orleans, Louisiana, 2001.
29. Lim KO, Choi SJ, Pomara N, Wolkin A, Rotrosen JP. Reduced frontal white matter integrity in cocaine dependence: a controlled diffusion tensor imaging study. Biol Psychiatry 2002; 51: 890–895.
30. Kusumo KS, Vaughan M. Effects of lithium salts on memory. Br J Psychiatry 1977; 131: 453–457.
31. Coffman JA, Bornstein RA, Olson SC, Schwarzkopf SB, Nasrallah HA. Cognitive impairment and cerebral structure by MRI in bipolar disorder. Biol Psychiatry 1990; 27: 1188–1196.
32. van Gorp WG, Altshuler L, Theberge DC, Wilkins J, Dixon W. Cognitive impairment in euthymic bipolar patients with and without prior alcohol dependence. A preliminary study. Arch Gen Psychiatry 1998; 55: 41–46.
33. Ferrier IN, Stanton BR, Kelly TP, Scott J. Neuropsychological function in euthymic patients with bipolar disorder. Br J Psychiatry 1999; 175: 246–251.
34. Adler CM, Strakowski SM. A parametric study of working memory in bipolar disorder. Presented at Society of Biological Psychiatry, New Orleans, Louisiana, 2001.
35. Manoach DS, Press DZ, Thangaraj V et al. Schizophrenic subjects activate dorsolateral prefrontal cortex during a working memory task, as measured by fMRI. Biol Psychiatry 1999; 45: 1128–1137.
36. Foong J, Maier M, Clark CA, Baker GJ, Miller DH, Ron MA. Neuropathological abnormalities of the corpus callosum in schizophrenia: A diffusion tensor imaging study. Neurol Neurosurg Psychiatry 2000; 68: 242–244.
37. Agartz I, Andersson JLR, Skare S. Abnormal brain white matter in schizophrenia: A diffusion tensor imaging study. Neuroreport 2001; 12: 2251–2254.
38. Virta A, Barnett A, Pierpaoli C. Visualizing and characterizing white matter fiber structure and architecture in the

human pyramidal tract using diffusion tensor MRI. Magn Reson Imaging 1999; 17: 1121–1133.
39. Sullivan EV, Adalsteinsson E, Hedehus M et al. Equivalent disruption of regional white matter microstructure in ageing healthy men and women. Neuroreport 2001; 12: 99–104.
40. Coffey CE, Saxton JA, Ratcliff G, Bryan RN, Lucke JF. Relation of education to brain size in normal aging: implications for the reserve hypothesis. Neurology 1999; 53: 189–196.
41. Meguro K, Shimada M, Yamaguchi S et al. Cognitive function and frontal lobe atrophy in normal elderly adults: implications for dementia not as aging-related disorders and the reserve hypothesis. Psychiatry Clin Neurosci 2001; 55: 565–572.