Eur Arch Psychiatry Clin Neurosci (2005) 255 : 313–318 DOI 10.1007/s00406-005-0564-z

ORIGINAL PAPER

Hideaki Kitamura · Hitoshi Matsuzawa · Toshiki Shioiri · Toshiyuki Someya · Ingrid L. Kwee · Tsutomu Nakada

Diffusion tensor analysis in chronic schizophrenia
A preliminary study on a high-field (3.0T) system

Received: 13 April 2004 / Accepted: 3 November 2004 / Published online: 14 January 2005

Abstract The objective of this study was to delineate further the nature of diffusion anisotropy abnormalities in frontal white matter previously observed in schizophrenic patients using a high-field magnetic resonance imaging (MRI) system. Six schizophrenia patients and six healthy control subjects were examined using a high-field MRI (3.0T) system. In order to confirm previously reported abnormalities in anisotropy, data were first analyzed to determine fractional anisotropy (FA), a frequently utilized general index of anisotropy. Subsequently, the identical data set was subjected to lambda chart analysis (LCA), a newly developed algorithm for diffusion tensor analysis (DTA) that more effectively provides eigenvalue information. Frontal white matter FA was found to be significantly reduced in schizophrenic patients compared to control subjects, confirming previously reported findings. LCA revealed that the decline in FA was due to a disproportionate increase in small eigenvalue components, and not due to a decline in principal eigenvalue components.

Key words schizophrenia · frontal lobe · magnetic resonance imaging (MRI) · diffusion tensor imaging (DTI) · lambda chart analysis (LCA)

H. Kitamura · H. Matsuzawa · T. Nakada, M. D., Ph. D. (✉)
Center for Integrated Human Brain Science
Brain Research Institute
University of Niigata
1 Asahimachi
Niigata 951–8585, Japan
Tel.: +81-25/227-0677
Fax: +81-25/227-0821
E-Mail: tnakada@bri.niigata-u.ac.jp

H. Kitamura · T. Shioiri · T. Someya
Dept. of Psychiatry
Graduate School of Medical and Dental Sciences
University of Niigata

I. L. Kwee · T. Nakada
Dept. of Neurology
University of California, Davis

Introduction

There is a considerable amount of indirect evidence suggesting that aberrant neuronal connectivity may play a significant role in the pathogenesis of schizophrenia (Andreasen et al. 1996; Friston 1998; McGlashan and Hoffman 2000; Weinberger et al. 1992). Various functional imaging studies have indicated diminished fronto-temporal coherent activities in schizophrenics (Frith et al. 1995; Fletcher et al. 1996; Mallet et al. 1998; Meyer-Lindenberg et al. 2001; Erkwoh et al. 1999). Magnetic resonance imaging (MRI) volumetry of white matter has revealed volume reductions of prefrontal (Breier et al. 1992; Bryant et al. 1999) and total white matter (Cannon et al. 1998) in schizophrenics. Diffusion tensor analysis (DTA) reported reduced diffusion anisotropy in prefrontal white matter (Buchsbaum et al. 1998), white matter in general (Lim et al. 1999), splenium of the corpus callosum (Agartz et al. 2001; Foong et al. 2000), arcuate fasciculus (Burns et al. 2003), and uncinate fasciculus (Burns et al. 2003; Kubicki et al. 2002) in schizophrenics. The results of these various studies strongly suggest further detailed analysis of white matter connectivity in schizophrenics.

DTA yields three independent quantitative values (eigenvalues). For simplicity, however, anisotropic analysis is generally performed utilizing certain indices calculated from three eigenvalues, such as anisotropy (FA) (Pierpaoli et al. 1996), relative anisotropy (RA) (Basser and Pierpaoli 1996), apparent anisotropy (AA) (van Gelderen et al. 1994), or trichromatic coefficients (TC) (Nakada and Matsuzawa 1995). Among them, FA represents the most widely utilized index. While index oriented relative anisotropy analysis is convenient, such analysis does not provide information regarding the behavior of each eigenvalue. One obvious solution is to examine all three original eigenvalues derived from diffusion tensor. However, such analysis is unnecessarily cumbersome and may not necessarily be beneficial in certain clinical investigations where significant fluctua-

tion of estimated eigenvalues would be inevitable, partially due to technical difficulties, and in part due to pathological variation of subjects. A technique has been introduced to partially overcome this confounding conflict, lambda chart analysis (LCA), which defines lambda longitudinal (λ_L) and lambda transverse (λ_T) (Matsuzawa and Nakada 2000).

Recent development of higher field systems has opened a new window for clinical investigation using MRI (Fujii et al. 1998; Hunsche et al. 2001; Kwee et al. 1999; Nakada et al. 2001, 2003). While higher susceptibility effects inherent to higher field systems can be a potential negative for DTA, the significant increase in signal to noise ratio (S/N), as much as a 40 % increase compared to conventional 1.5T systems (Hunsche et al. 2001), is a significant advantage. In this study, we investigated the nature of the abnormalities in anisotropy of white matter diffusivity observed in schizophrenic patients by utilizing LCA on a 3.0T system.

Methods

Subjects

Six right-handed male outpatients, who met DSM-IV (APA 1994) criteria for schizophrenia and who had no other comorbid psychiatric illness or attendant neurologic disorders, were selected from the university hospital pool of clinic patients. A board-certified psychiatrist conducted semi-structured interviews including the Japanese version of the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al. 1992). The symptom profile of each patient was evaluated using the 18-item Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1988). All patients were on maintenance antipsychotic medications (Chlorpromazine equivalent of 727 ± 369 mg/day, range 300–1279 mg/day) (APA 1997) and had good symptom control. Six right-handed age-matched healthy adult male subjects, who had no psychiatric or neurologic diagnoses, were recruited from a local university community. Right-handedness was confirmed by the Edinburgh inventory (Oldfield 1971). Mean age was 31 ± 5.4 (range 24–38) for patients and 32 ± 4.3 (range 26–36) for controls. Alcohol consumption assessed through detailed interview and review of medical records, where available, was determined to be negligible for patients and controls. Education level was 14 ± 2.0 years (range 12–16 years) for patients and 18 ± 2.7 years (range 14–22 years) for controls. Parents' education was 13 ± 2.2 years (range 9–15 years) for patients and 14 ± 0.4 years (range 14–15 years) for controls. Mean duration of illness was 126 ± 75 months (range 40–245 months), and mean scores of BPRS was 34 ± 6 [23–39]. Subjects were imaged according to the human research guidelines of the Internal Review Board of the University of Niigata. Written informed consent was obtained from all twelve subjects.

Diffusion tensor imaging

A General Electric (Waukesha, Wisconsin, USA) Signa 3.0 T system equipped with an Advanced NMR echo planar imaging (EPI) module was used to perform all the studies. In order to minimize artificial effects due to potential head motion, especially in patients, we employed an EPI sequence of diffusion tensor imaging instead of gating. Diffusion weighted images were acquired with modified tetrahedral EPI sequences using the following parameter settings: axial slices 5; FOV 200 mm × 200 mm; matrix 64 × 64; slice thickness 5 mm; interslice gaps 2.5 mm; repetition time (TR) 2.5 s; effective echo time (TE) 153 ms; number of excitation (NEX) 16; b-value 800 s/mm^2. Parameters for motion probing gradient (MPG) utilized were: amplitude 7.2 mT/m; ramp time 600 μs; $\Delta = 56.7$ ms; $\delta = 52.6$ ms. MPGs were always applied on 2 axes simultaneously. Six non-collinear directions of the gradients (Gx, Gy, Gz) were as follows: (1, 1, 0), (0, 1, 1), (1, 0, 1), (–1, 1, 0), (0, –1, 1), (1, 0, –1), where (Gx, Gy, Gz) direction corresponded to (read-out, phase, slice). Eddy current compensation has been performed at the hardware level by in-house engineers who perform daily optimization work on all installed MR systems at our institute and no software correction for individual studies is needed. For each gradient direction, including no diffusion weighting, 16 diffusion-weighted images were acquired and averaged for calculation of the eigenvalues. Total imaging time for acquisition of the entire diffusion imaging data set was 5 minutes.

Data analysis

An axial slice passing through the body of the corpus callosum was selected for analysis. Small regions of interest consisting of four voxels (6.25 × 6.25 × 5 mm^3) were selected in frontal and parietal white matter bilaterally in each slice (Fig. 1), without contamination of other tissue types. Numerical data were analyzed on an Ultra 60 workstation (Sun Microsystems, Mountain View, CA). Eigenvalues ($\lambda_1 > \lambda_2 > \lambda_3$) were determined using Mathematica version 3.0E (Wolfram Research, Inc.).

A detailed description of lambda chart analysis (LCA) is beyond the scope of this report. In brief, LCA is an algorithm for analyzing brain anisotropy based on the widely accepted observation that diffusion anisotropy of the brain arises almost exclusively from neuronal fibers, principally axons. This biological constraint immediately provides the axiomatic condition that anisotropy should be observed only in one direction: $\lambda_1 \geq \lambda_2 = \lambda_3$. The concept is shown schematically in Fig. 2. Accordingly, a biological diffusion system of interest such as neuronal axons can be characterized by the diffusion characteristic function, $\Psi(Tr, \theta)$, where Tr represents the trace and θ the anisotropic angle. Numerical data for statistical analysis are obtained through expressing the diffusion system in question by its two eigenvalues, lambda longitudinal (λ_L) and lambda transverse (λ_T), which can be given as

$$\lambda_L = \lambda_1$$
$$\lambda_T = \frac{\lambda_2 + \lambda_3}{2}$$

For confirmation purposes, a commonly utilized relative anisotropy index, fractional anisotropy (FA) (Pierpaoli et al. 1996), was also determined. It is self evident by definition that λ_L has a positive effect and λ_T a negative effect on FA.

Student's *t*-test was used to assess group differences of demographic variables, FA, λ_L, and λ_T. In addition, separate 2-way repeated-measures analysis of variance (ANOVA) was applied for evaluating diagnostic and regional main effects of diffusion measures and any interaction between them. All statistical analyses were performed using SPSS 9.0J for Windows (SPSS Japan Inc.). Bonferroni corrections for t-test between controls and patients in each white matter region and for t-test between frontal WM and parietal WM in each diagnostic group were applied by dividing the α level by number of comparisons, 4 (adjusted $\alpha = 0.0125$). Similarly, the p value in ANOVA was set to less than 0.05, because we considered FA, λ_L, and λ_T as mutually independent diffusion measures.

Results

Fig. 2 demonstrates representative LCA of frontal white matter. Characteristic deviation of diffusion characteristics of frontal white matter in schizophrenic patients is clearly observed. For better presentation, the numerical data of λ_L and λ_T were individually analyzed statistically and shown in Fig. 3 along with the results of statistical analysis for FA. λ_L and λ_T were both significantly *in-*

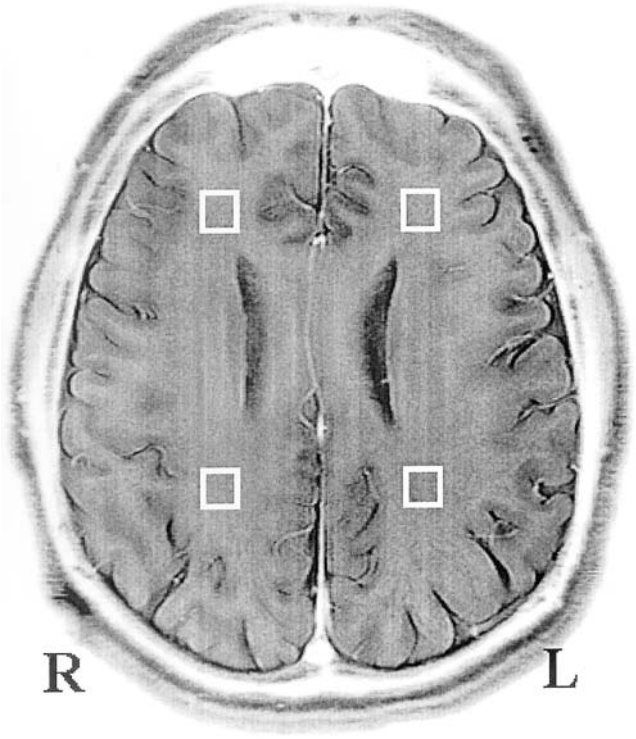

Fig. 1 Regions of interest (ROIs) utilized

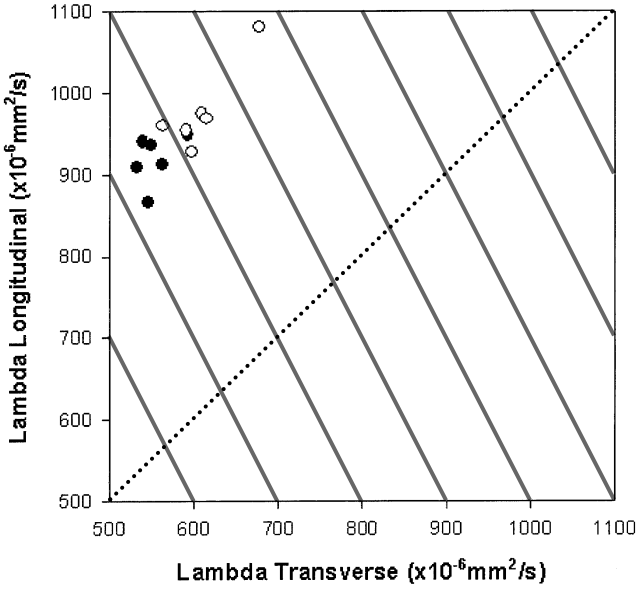

Fig. 2 Lambda chart analysis of frontal white matter. Each point indicates data from individual subject's frontal ROI (Data from left and right ROIs are averaged). X-axis is for lambda longitudinal (λ_L), Y-axis is for lambda transverse (λ_T). White circles for schizophrenic patients, black circles for healthy controls. Note that the diffusion characteristics of schizophrenia patients deviates towards higher trace direction almost parallel to the isotropic line (dotted line), perpendicularly crossing isotrace lines (grey lines)

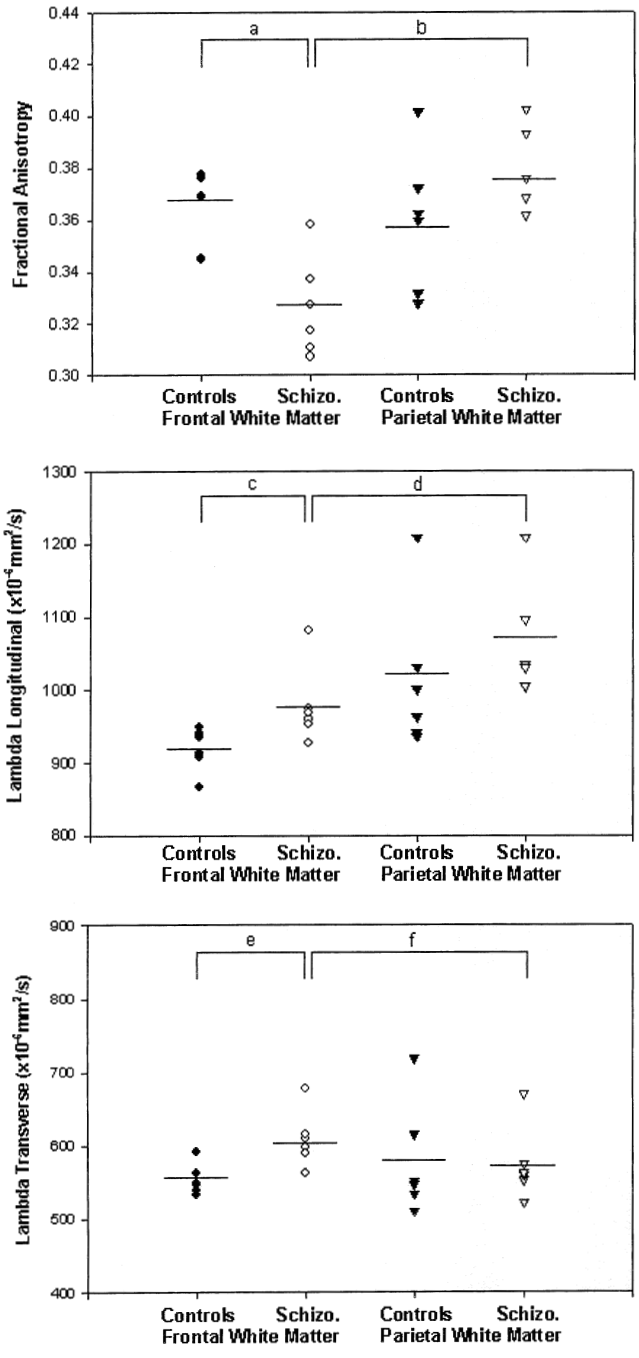

Fig. 3 Graphical summary of results. **a** $p = 0.004$ (t-test, $t = 3.79$, $df = 10$), **b** $p = 0.006$ (paired t-test, $t = -4.52$, $df = 5$), **c** $p = 0.041$ (t-test, $t = -2.34$, $df = 10$), **d** $p = 0.001$ (paired t-test, $t = -6.42$, $df = 5$), **e** $p = 0.012$ (t-test, $t = -3.08$, $df = 10$), **f** $p = 0.019$ (paired t-test, $t = 3.41$, $df = 5$)

creased to the same degree in frontal white matter of schizophrenic patients compared to control subjects. In contrast, FA was significantly *decreased* in frontal white matter of schizophrenic patients compared to control subjects. Table 1 shows that ANOVA yields significant main effects for diagnosis (λ_L) and region (FA, λ_L), and an interaction between diagnosis and region (FA, λ_T). There were no significant correlations between clinical variables and any diffusion measures ($p > 0.10$).

Table 1 Three separate 2-way repeated-measures analyses of variance for diffusion measures of control subjects (n = 6) and patients with schizophrenia (n = 6)

Diffusion measures	Frontal white matter	Parietal white matter	Diagnosis effect (D)	Region effect (R)	D × R interaction
Fractional anisotropy (FA)					
Control	0.364 ± 0.014	0.359 ± 0.027	0.094	6.063[a]	8.591[b]
Schizophrenia	0.326 ± 0.019	0.378 ± 0.016			
Lambda longitudinal ($\times 10^{-6}$: λ_L)					
Control	919.0 ± 30.1	1013.6 ± 102.0	10.328[c]	20.252[d]	0.292
Schizophrenia	977.7 ± 53.5	1063.1 ± 78.5			
Lambda transverse ($\times 10^{-6}$: λ_T)					
Control	553.8 ± 21.4	579.5 ± 76.6	3.497	0.270	7.439[e]
Schizophrenia	608.8 ± 38.3	573.9 ± 50.3			

Mean ± SD and F-values (df = 1, 94) for each diffusion measure
[a] p = 0.016 for the region effect on FA
[b] p = 0.004 for the interaction between diagnosis and region on FA
[c] p = 0.002 for the diagnosis effect on λL
[d] p = 0.000 for the region effect on λL
[e] p = 0.008 for the interaction between diagnosis and region on λT

Discussion

Our study confirms previous reports by others that anisotropy is reduced in white matter of patients with schizophrenia when compared to comparison subjects (Agartz et al. 2001; Buchsbaum et al. 1998; Burns et al. 2003; Foong et al. 2000; Kubicki et al. 2002; Lim et al. 1999). Our finding is also highly consistent with previous studies suggesting frontostriatal (Buchsbaum et al. 1998) or frontotemporal (Kubicki et al. 2002; Burns et al. 2003) disconnection in the disease. Our study further demonstrated that the observed decline in frontal white matter FA was due to a disproportionate *increase* of the small eigenvalue components (λ_T) and *not* due to a *decline* in principal eigenvalue (λ_L).

Although speculative, one of the most plausible explanations for the pattern of eigenvalue alterations observed in schizophrenics in this study is an increase in unrestricted water contents in the extra-axonal space (Fig. 4A). Extra-axonal free water has *isotropic* behavior and, hence, an increase in the relative volume of this space results in an *increase* of all eigenvalues to the same degree. Since the largest eigenvalue is further affected by *anisotropic* behavior of intra-axonal water, the percent increase in volume will affect the transverse eigenvalue (λ_T) to a greater extent than the longitudinal eigenvalue (λ_L). Intra-axonal physiology such as axoplasmic flow mainly affects λ_L; however, this effect may be inadvertently obscured by concomitant alterations in extra-axonal space. A post-mortem study (Highley et al. 1999) reporting reduced density of axonal fibers in the anterior commissure supports the above inference about relative volume change between intra- and extra-axonal spaces in schizophrenia. This finding implies that expansion of the extra-axonal space in frontal white matter may play a significant role in the pathogenesis of schizophrenia. To our surprise, the reversed pattern in frontal white matter diffusivity was found in our laboratory as the typical pattern for physiological maturation (Fig. 4B) (Suzuki et al. 2003). The observation suggests that frontal white matter in schizophrenics indeed shows mild disorders similar to white matter undergoing maturation.

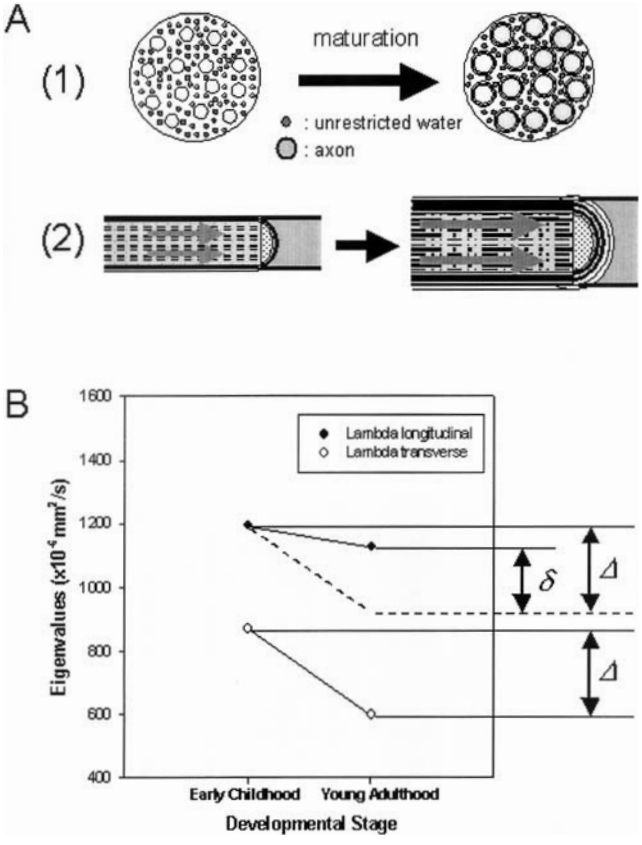

Fig. 4 Schema showing known micro-environmental alterations during the myelination period and their relationship to characteristic changes in eigenvalue. **A** Schematic presentation of maturational changes, the characteristics of which include [1] decline in free extra axonal water and [2] increase in axoplasmic flow. **B** Corresponding alteration in diffusion characteristics. While both λ_L and λ_T decline according to the decline in free extra-axonal water (Δ), λ_L showed a fractional increase related to an increase in axoplasmic flow (δ)

We recognize several limitations of the study. Since ROI comprises white matter in the frontal association area, orientation of individual axonal fibers within the ROI is multi-directional. The possibility remains that averaged values of diffusion measures simply reflect the degree of multi-directionality of axonal fibers. The results of this study could be interpreted to reflect a degenerative process such as demyelination. A growing body of evidence suggests the presence of myelin abnormalities in schizophrenia (Davis et al. 2003). The disease process underlying schizophrenia may alter normal axonal circuits to effect high diffusivity similar to immature brain. Additional studies are needed to elucidate the specific nature of white matter abnormalities in schizophrenia.

Acknowledgments The study was supported by grants from the Ministry of Education, Culture, Sports, Science, and Technology (Japan).

References

1. Agartz I, Andersson JL, Skare S (2001) Abnormal brain white matter in schizophrenia: a diffusion tensor imaging study. Neuroreport 12:2251–2254
2. American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders, 4th ed. APA, Washington DC
3. American Psychiatric Association (1997) Practical guideline for the treatment of patients with schizophrenia. III. Treatment principles and alternatives. Am J Psychiatry 154(Suppl):7–34
4. Andreasen NC, Flaum M, Arndt S (1992) The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. Arch Gen Psychiatry 49:615–623
5. Andreasen NC, O'Leary DS, Cizadlo T, Arndt S, Rezai K, Ponto LL, Watkins GL, Hichwa RD (1996) Schizophrenia and cognitive dysmetria: a positron-emission tomography study of dysfunctional prefrontal-thalamic-cerebellar circuitry. Proc Natl Acad Sci USA 93:9985–9990
6. Basser PJ, Pierpaoli C (1996) Microstructural and physiological features of tissues elucidated by Quantitative-Diffusion-Tensor MRI. J Magn Reson B 111:209–219
7. Breier A, Buchanan RW, Elkashef A, Munson RC, Kirkpatrick B, Gellad F (1992) Brain morphology and schizophrenia. A magnetic resonance imaging study of limbic, prefrontal cortex, and caudate structures. Arch Gen Psychiatry 49:921–926
8. Bryant NL, Buchanan RW, Vladar K, Breier A, Rothman M (1999) Gender differences in temporal lobe structures of patients with schizophrenia: a volumetric MRI study. Am J Psychiatry 156: 603–609
9. Buchsbaum MS, Tang CY, Peled S, Gudbjartsson H, Lu D, Hazlett EA, Downhill J, Haznedar M, Fallon JH, Atlas SW (1998) MRI white matter diffusion anisotropy and PET metabolic rate in schizophrenia. Neuroreport 9:425–430
10. Burns J, Job D, Bastin ME, Whalley H, Macgillivray T, Johnstone EC, Lawrie SM (2003) Structural disconnectivity in schizophrenia: a diffusion tensor magnetic resonance imaging study. Br J Psychiatry 182:439–443
11. Cannon TD, van Erp TG, Huttunen M, Lonnqvist J, Salonen O, Valanne L, Poutanen VP, Standertskjold-Nordenstam CG, Gur RE, Yan M (1998) Regional gray matter, white matter, and cerebrospinal fluid distributions in schizophrenic patients, their siblings, and controls. Arch Gen Psychiatry 55:1084–1091
12. Davis KL, Stewart DG, Friedman JI, Buchsbaum M, Harvey PD, Hof PR, Buxbaum J, Haroutunian V (2003) White matter changes in schizophrenia: evidence for myelin-related dysfunction. Arch Gen Psychiatry 60:443–456
13. Erkwoh R, Sabri O, Willmes K, Steinmeyer EM, Bull U, Sass H (1999) Aspects of cerebral connectivity in schizophrenia. A comparative CBF study on treated schizophrenics before and after medication. Fortschr Neurol Psychiatr 67:318–326
14. Fletcher PC, Frith CD, Grasby PM, Friston KJ, Dolan RJ (1996) Local and distributed effects of apomorphine on fronto-temporal function in acute unmedicated schizophrenia. J Neurosci 16: 7055–7062
15. Foong J, Maier M, Clark CA, Barker GJ, Miller DH, Ron MA (2000) Neuropathological abnormalities of the corpus callosum in schizophrenia: a diffusion tensor imaging study. J Neurol Neurosurg Psychiatry 68:242–244
16. Friston KJ (1998) The disconnection hypothesis. Schizophr Res 30:115–125
17. Frith CD, Friston KJ, Herold S, Silbersweig D, Fletcher P, Cahill C, Dolan RJ, Frackowiak RS, Liddle PF (1995) Regional brain activity in chronic schizophrenic patients during the performance of a verbal fluency task. Br J Psychiatry 167:343–349
18. Fujii Y, Nakayama N, Nakada T (1998) High-resolution T2 reversed magnetic resonance imaging on high magnetic field system. J Neurosurg 89:492–495
19. Highley JR, Esiri MM, McDonald B, Roberts HC, Walker MA, Crow TJ (1999) The size and fiber composition of the anterior commissure with respect to gender and schizophrenia. Biol Psychiatry 45:1120–1127
20. Hunsche S, Moseley ME, Stoeter P, Hedehus M (2001) Diffusion-tensor MR imaging at 1.5 and 3.0 T: initial observations. Radiology 221:550–556
21. Kubicki M, Westin CF, Maier SE, Frumin M, Nestor PG, Salisbury DF, Kikinis R, Jolesz FA, McCarley RW, Shenton ME (2002) Uncinate fasciculus findings in schizophrenia: a magnetic resonance diffusion tensor imaging study. Am J Psychiatry 159:813–820
22. Kwee IL, Fujii Y, Matsuzawa H, Nakada T (1999) Perceptual processing of stereopsis in human: High-field (3.0T) functional MRI study. Neurology 53:1599–1601
23. Lim KO, Hedehus M, Moseley M, de Crespigny A, Sullivan EV, Pfefferbaum A (1999) Compromised white matter tract integrity in schizophrenia inferred from diffusion tensor imaging. Arch Gen Psychiatry 56:367–374
24. Mallet L, Mazoyer B, Martinot JL (1998) Functional connectivity in depressive, obsessive-compulsive, and schizophrenic disorders: an explorative correlational analysis of regional cerebral metabolism. Psychiatry Res 82:83–93
25. Matsuzawa H, Nakada T (2000) Lambda chart analysis and eigenvalue imaging. In: Nakada T (ed) Integrated Human Brain Science: Theory, Method, Application (Music). Elsevier, Amsterdam, pp 219–225
26. McGlashan TH, Hoffman RE (2000) Schizophrenia as a disorder of developmentally reduced synaptic connectivity. Arch Gen Psychiatry 57:637–648
27. Meyer-Lindenberg A, Poline JB, Kohn PD, Holt JL, Egan MF, Weinberger DR, Berman KF (2001) Evidence for abnormal cortical functional connectivity during working memory in schizophrenia. Am J Psychiatry 158:1809–1817
28. Nakada T, Matsuzawa H (1995) Three-dimensional anisotropy contrast magnetic resonance imaging of the rat nervous system: MR axonography. Neurosci Res 22:389–398
29. Nakada T, Fujii Y, Yoneoka Y, Kwee IL (2001) Planum temporale where spoken and written language meet. Eur Neurol 46:121–125
30. Nakada T (2003) Clinical Experience on 3.0T Systems in Niigata: 1996–2002. Invest Radiol 38:377–384
31. Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97–113
32. Overall JE, Gorham DR (1988) The Brief Psychiatric Rating Scale (BPRS): recent developments in ascertainment and scaling. Psychopharmacol Bull 24:97–99
33. Pierpaoli C, Jezzard P, Basser PJ, Barnett A, Di Chiro G (1996) Diffusion tensor MR imaging of the human brain. Radiology 201: 637–648

34. Suzuki Y, Matsuzawa H, Kwee IL, Nakada T (2003) Absolute eigenvalue diffusion tensor analysis for human brain maturation. NMR Biomed 16:257–260
35. van Gelderen P, de Vleeschouwer MHM, DesPres D, Pekar J, van Zijl PCM, Moonen CTW (1994) Water diffusion and acute stroke. Magn Reson Med 31:154–163
36. Weinberger DR, Berman KF, Suddath R, Torrey EF (1992) Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: a magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins. Am J Psychiatry 149:890–897