assessed first-episode schizophrenia and reported lower FA values in the patients as compared to controls at widespread brain regions, including the cerebral peduncle.[2,3] Some studies conducted in schizophrenic patients demonstrated significantly lower FA than in controls in the cerebellum.[28,29] In the present study, plasma MHPG was significantly higher at follow-up than at baseline. This indicates that the FA value in the cerebellum, which has a positive correlation with plasma MHPG, may have increased over the follow-up interval, probably due to the effect of antipsychotic drug treatment.

The neurodegenerative hypothesis in schizophrenia suggests that pathologic alterations in brain morphology may occur after onset of the illness, mainly in the early stages, and may be associated with the illness' course and severity.[30] This hypothesis is supported by both longitudinal clinical and neuroimaging studies after onset.[1,31] Several prospective longitudinal studies in first-episode schizophrenia found progressive volume reduction at the initial stage of schizophrenia in the frontal and temporal areas, especially the superior temporal gyrus, Heschl's gyrus, and amygdala–hippocampal complex;[1,32,33] more pronounced volume reduction in these areas was associated with poor outcome, negative symptoms, and a decline in neuropsychological performance.[31,33] Furthermore, progressive reduction in cerebellum volume has also been reported in first-episode schizophrenia. In contradiction to this previous study, our results indicate that the FA changes (microstructural tissue alteration) within the cerebellum can be normalized during the early stage of first-episode schizophrenia.

Moreover, our results may also suggest that microstructural changes (FA changes) within the cerebellum relate to norepinephrine activity during the early stage of first-episode schizophrenia. Many regions of the brain are supplied by the noradrenergic systems. The principal centers for noradrenergic neurons are the locus coeruleus and the caudal raphe nuclei. The ascending nerves of the locus coeruleus project to the frontal cortex, thalamus, hypothalamus, and limbic system. Noradrenaline is also transmitted from the locus coeruleus to the cerebellum. Our positive correlation between the FA in the cerebellar vermis and norepinephrine metabolite MHPG may reflect these functional connections in the cerebellum as noradrenergic systems.

Traditionally, the emphasis of studies on cerebellar function has been on the coordination of somatic motor function, control of muscle tone, and equilibrium. However, the cerebellum also shares bidirectional connections with a large portion of the limbic lobe and the associated subcortical nuclei, the amygdaloid complex, the septal nuclei, and various hypothalamic and thalamic nuclei, which are regions of interest to psychiatry through their association with emotional processing. There is accumulating evidence of a cognitive role of the cerebellum,[30] including executive function and working memory, which are impaired in schizophrenia.[31] The previous neuroimaging studies by the resting-state functional MRI[34,35] and DTI method[28,29] suggest that the connectivity of the cerebellum is impaired in schizophrenia. Collin et al[34] demonstrated that, compared to healthy control subjects, schizophrenia patients showed impaired functional connectivity between the cerebellum and several cerebral regions, including the hippocampus, thalamus, middle cingulate gyrus, triangular part of the inferior frontal gyrus, supplementary motor area, and lingual gyrus. Furthermore, Liu et al[35] found that in schizophrenic patients, the bilateral cerebellum showed reduced functional connectivities to some regions compared to controls, such as the left middle temporal gyrus, bilateral middle cingulate cortex, right paracentral lobule, right thalamus, and bilateral cerebellum, and the FA of the left superior cerebellar peduncles was significantly reduced in patients. These results also support the opinion that the cerebellum might play a key role in schizophrenia.

Andreasen et al and Wiser et al proposed that disruption of a cortico–cerebellar–thalamic–cortical circuit (CCTCC) may underlie the combination of symptoms observed in schizophrenia.[36,37] This model of schizophrenia as secondary to disrupted development in the CCTCC has been termed 'cognitive dysmetria',[37] referring to incoordination in the processing, prioritization, retrieval, and expression of information. Our finding that the microstructural changes in the cerebellum occurred during 6-month follow-up in patients with first-episode schizophrenia may be consistent with theoretical accounts of schizophrenia as a disorder of functional integration, and with the cognitive dysmetria hypothesis, which posits a disconnection within the CCTCC as a fundamental abnormality in schizophrenia.

Recent studies have reported the relationship between MRI data and the PANSS. One study reported that a small area of white matter near the right insula showed a positive correlation between the PANSS negative symptoms and apparent diffusion coefficient.[38] Another study demonstrated that the positive correlation of FA values with positive symptom scores were seen in the white matter adjacent to the right lateral ventricle, and also found an inverse correlation between FA values in the same brain region and negative symptom scores.[6] To the best of our knowledge, however, no previous MRI studies have reported

the longitudinal relationship between MRI data and the PANSS in schizophrenic patients. Although the PANSS was improved significantly over the follow-up interval by ongoing antipsychotic drug treatment, correlations between longitudinal MR data and PANSS changes were not found in any brain regions. Therefore, clinical improvement may not necessarily be related to the microstructural changes of the brain. Whitford et al have reported the evidence of progressive white matter atrophy over the first 2–3 years of illness in patients with first-episode schizophrenia, although the psychotic symptoms (PANSS) in these patients improved over this interval.[39] The results from these previous studies may support our negative data.

There were several limitations to this study. Firstly, the number of patients was small. Although previous MR studies have reported the cerebellar volume abnormalities in schizophrenia patients,[40,41] our study did not show any correlation between brain volume and laboratory data in any brain region. Furthermore, in this study, the correlations between the longitudinal MR data and PANSS changes were not found in any brain regions. Therefore, our small sample size might limit the statistical power in these analyses. Secondly, our patients received various kinds of antipsychotic medication at baseline MR examinations, which may have affected the MR data and peripheral catecholaminergic measures. The DUP classically refers to the duration of untreated psychosis. In this sense, the value of DUP in the present study may not be precise, because the patients had been administered antipsychotic drugs before they underwent baseline MRI. However, it could be ethically problematic to follow the psychotic patients without any antipsychotic drugs until performing an MR examination. Thirdly, the initial symptoms of schizophrenia might start before the patients and their family notice a problem. Finally, the heterogeneity of our sample population may exist by the inclusion of a wide age range or clinical variables, such as disorganization score and intelligence quotient (IQ), in comparison with a previous study.[5,30,42–44] Although DeLisi et al reported that approximately 60% of plasma MHPG is derived from the brain,[42] it is currently believed that about one-third of plasma MHPG is of brain origin.[45] In short, we should note with caution the use of plasma MHPG as an indicator of activities in central noradrenergic neurons as it is predominantly derived from the periphery.

Conclusion

We found evidence that patients with first-episode schizophrenia exhibit a positive correlation of interval changes between the FA in the right cerebellar vermis and the norepinephrine metabolite MHPG during 6-month follow-up; this may reflect both anatomic and functional connections within the cerebellum to the prefrontal cortex, the subcortical limbic structures, and monoamine-producing brainstem nuclei. Our findings also suggest that microstructural FA changes could be reversible during the early stage of first-episode schizophrenia, and that plasma MHPG might therefore be a sensitive marker for the detection of this change.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Shenton ME, Dickey CC, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. *Schizophr Res*. 2001;49(1–2):1–52.
2. Cheung V, Cheung C, McAlonan GM, et al. A diffusion tensor imaging study of structural dysconnectivity in never-medicated, first-episode schizophrenia. *Psychol Med*. 2008;38(6):877–885.
3. Hao Y, Liu Z, Jiang T, et al. White matter integrity of the whole brain is disrupted in first-episode schizophrenia. *Neuroreport*. 2006;17(1):23–26.
4. Jayakumar PN, Venkatasubramanian G, Gangadhar BN, Janakiramaiah N, Keshavan MS. Optimized voxel-based morphometry of gray matter volume in first-episode, antipsychotic-naive schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005;29(4):587–591.
5. Szeszko PR, Ardekani BA, Ashtari M, et al. White matter abnormalities in first-episode schizophrenia or schizoaffective disorder: a diffusion tensor imaging study. *Am J Psychiatry*. 2005;162(3):602–605.
6. Moriya J, Kakeda S, Abe O, et al. Gray and white matter volumetric and diffusion tensor imaging (DTI) analyses in the early stage of first-episode schizophrenia. *Schizophr Res*. 2010;116(2):196–203.
7. Skelly LR, Calhoun V, Meda SA, Kim J, Mathalon DH, Pearlson GD. Diffusion tensor imaging in schizophrenia: relationship to symptoms. *Schizophr Res*. 2008;98(1):157–162.
8. Hornykiewicz O. Brain catecholamines in schizophrenia – a good case for noradrenaline. *Nature*. 1982;299(5883):484–486.
9. van Kammen DP, Agren H, Yao JK, O'Connor DT, Gurklis J, Peters JL. Noradrenergic activity and prediction of psychotic relapse following haloperidol withdrawal in schizophrenia. *Am J Psychiatry*. 1994;151(3):379–384.
10. Yoshimura R, Nakamura J, Ueda N, Terao T. Effect of risperidone on plasma free 3-methoxy-4-hydroxyphenylglycol (pMHPG) levels in schizophrenic patients: relationship among plasma concentrations of risperidone and 9-hydroxyrisperidone, pMHPG levels, and clinical improvement. *Int Clin Psychopharmacol*. 2000;15(3):175–180.
11. Yoshimura R, Ueda N, Shinkai K, Nakamura J. Plasma levels of homovanillic acid and the response to risperidone in first episode untreated acute schizophrenia. *Int Clin Psychopharmacol*. 2003;18(2):107–111.
12. Kakihara S, Yoshimura R, Shinkai K, et al. Prediction of response to risperidone treatment with respect to plasma concencentrations of risperidone, catecholamine metabolites, and polymorphism of cytochrome P450 2D6. *Int Clin Psychopharmacol*. 2005;20(2):71–78.
13. Yoshimura R, Yanagihara N, Hara K, et al. Inhibitory effects of clozapine and other antipsychotic drugs on noradrenaline transporter in cultured bovine adrenal medullary cells. *Psychopharmacology (Berl)*. 2000;149(1):17–23.
14. Hori H, Yoshimura R, Yamada Y, et al. Effects of olanzapine on plasma levels of catecholamine metabolites, cytokines, and brain-derived neurotrophic factor in schizophrenic patients. *Int Clin Psychopharmacol*. 2007;22(1):21–27.

15. Jovicich J, Czanner S, Greve D, et al. Reliability in multi-site structural MRI studies: effects of gradient non-linearity correction on phantom and human data. *Neuroimage*. 2006;30(2):436–443.
16. Sled JG, Zijdenbos AP, Evans AC. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Med Imaging*. 1998;17(1):87–97.
17. Ashburner J, Friston KJ. Voxel-based morphometry – the methods. *Neuroimage*. 2000;11(6 Pt 1):805–821.
18. Ashburner J, Friston KJ. Unified segmentation. *Neuroimage*. 2005; 26(3):839–851.
19. Ashburner J. A fast diffeomorphic image registration algorithm. *Neuroimage*. 2007;38(1):95–113.
20. Abe O, Yamasue H, Aoki S, et al. Aging in the CNS: comparison of gray/white matter volume and diffusion tensor data. *Neurobiol Aging*. 2008;29(1):102–116.
21. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*. 2002;17(2):825–841.
22. Luders E, Gaser C, Jancke L, Schlaug G. A voxel-based approach to gray matter asymmetries. *Neuroimage*. 2004;22(2):656–664.
23. Yung AR, Phillips LJ, Yuen HP, et al. Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. *Schizophr Res*. 2003; 60(1):21–32.
24. Ohnishi A, Minegishi A, Ishizaki T. Effect of [beta]-adrenoceptor blockade on exercise-induced plasma catecholamine concentration-heart rate response relationship. *J Cardiovasc Pharmacol*. 1987;10(6): 667–674.
25. Tan HY, Ang YG. First-episode psychosis in the military: a comparative study of prodromal symptoms. *Aust N Z J Psychiatry*. 2001;35(4): 512–519.
26. McGlashan TH. A selective review of recent North American long-term followup studies of schizophrenia. *Schizophr Bull*. 1988;14(4): 515–542.
27. McGlashan TH. Early detection and intervention of schizophrenia: rationale and research. *Br J Psychiatry Suppl*. 1998;172(33):3–6.
28. Kyriakopoulos M, Frangou S. Recent diffusion tensor imaging findings in early stages of schizophrenia. *Curr Opin Psychiatry*. 2009;22(2): 168–176.
29. Kanaan RA, Borgwardt S, McGuire PK, et al. Microstructural organization of cerebellar tracts in schizophrenia. *Biol Psychiatry*. 2009;66(11): 1067–1069.
30. Kakeda S, Korogi Y. The efficacy of a voxel-based morphometry on the analysis of imaging in schizophrenia, temporal lobe epilepsy, and Alzheimer's disease/mild cognitive impairment: a review. *Neuroradiology*. 2010;52(8):711–721.
31. Hulshoff Pol HE, Kahn RS. What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. *Schizophr Bull*. 2008;34(2):354–366.
32. Asami T, Bouix S, Whitford TJ, Shenton ME, Salisbury DF, McCarley RW. Longitudinal loss of gray matter volume in patients with first-episode schizophrenia: DARTEL automated analysis and ROI validation. *Neuroimage*. 2012;59(2):986–996.
33. Yoshida T, McCarley RW, Nakamura M, et al. A prospective longitudinal volumetric MRI study of superior temporal gyrus gray matter and amygdala-hippocampal complex in chronic schizophrenia. *Schizophr Res*. 2009;113(1):84–94.
34. Collin G, Hulshoff Pol HE, Haijma SV, Cahn W, Kahn RS, van den Heuvel MP. Impaired cerebellar functional connectivity in schizophrenia patients and their healthy siblings. *Front Psychiatry*. 2011;2:73.
35. Liu H, Fan G, Xu K, Wang F. Changes in cerebellar functional connectivity and anatomical connectivity in schizophrenia: a combined resting-state functional MRI and diffusion tensor imaging study. *J Magn Reson Imaging*. 2011;34(6):1430–1438.
36. Andreasen NC, O'Leary DS, Cizadlo T, et al. Schizophrenia and cognitive dysmetria: a positron-emission tomography study of dysfunctional prefrontal-thalamic-cerebellar circuitry. *Proc Natl Acad Sci U S A*. 1996; 93(18):9985–9990.
37. Wiser AK, Andreasen NC, O'Leary DS, Watkins GL, Boles Ponto LL, Hichwa RD. Dysfunctional cortico-cerebellar circuits cause 'cognitive dysmetria' in schizophrenia. *Neuroreport*. 1998;9(8):1895–1899.
38. Shin YW, Kwon JS, Ha TH, et al. Increased water diffusivity in the frontal and temporal cortices of schizophrenic patients. *Neuroimage*. 2006;30(4):1285–1291.
39. Whitford T, Grieve S, Farrow T, et al. Volumetric white matter abnormalities in first-episode schizophrenia: a longitudinal, tensor-based morphometry study. *Am J Psychiatry*. 2007;164(7):1082–1089.
40. Volz H, Gaser C, Sauer H. Supporting evidence for the model of cognitive dysmetria in schizophrenia – a structural magnetic resonance imaging study using deformation-based morphometry. *Schizophr Res*. 2000;46(1):45–56.
41. Levitt JJ, McCarley RW, Nestor PG, et al. Quantitative volumetric MRI study of the cerebellum and vermis in schizophrenia: clinical and cognitive correlates. *Am J Psychiatry*. 1999;156(7):1105–1107.
42. DeLisi LE, Sakuma M, Ge S, Kushner M. Association of brain structural change with the heterogeneous course of schizophrenia from early childhood through five years subsequent to a first hospitalization. *Psychiatry Res*. 1998;84(2–3):75–88.
43. Pantelis C, Yücel M, Wood SJ, et al. Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. *Schizophr Bull*. 2005;31(3):672–696.
44. Collin G, Derks E, van Haren N, et al. Symptom dimensions are associated with progressive brain volume changes in schizophrenia. *Schizophr Res*. 2012;138(2–3):171–176.
45. Nagaoka A, Shino A, Iwatsuka H. Accelerating effects of dexamethasone and thyroxine on hypertension without accompanying stroke in stroke-prone spontaneously hypertensive rats. *Life Sci*. 1979;24(1):71–77.

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Relationships between brain-derived neurotrophic factor, clinical symptoms, and decision-making in chronic schizophrenia: data from the Iowa Gambling Task

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The levels of brain-derived neurotrophic factor (BDNF) are significantly decreased in patients with schizophrenia and correlate with impairments in cognitive function. However, no study has investigated the relationship between the serum BDNF levels and decision-making. We compared patients with schizophrenia to healthy controls with respect to their decision-making ability and serum BDNF levels. Eighty-six chronic schizophrenia patients and 51 healthy controls participated in this study. We controlled for gender, age, and estimated intelligence quotient (IQ), and we investigated the differences in decision-making performance on the Iowa Gambling Task (IGT) between the schizophrenia patient and control groups. We also compared the IGT scores, the serum BDNF levels, and the clinical symptoms between the groups. The IGT scores of the schizophrenia patients were lower than those of the controls. A negative correlation was detected between the mean net scores on the trials in the final two blocks and the serum BDNF levels ($p < 0.05$). Multiple regression analysis revealed that depressive symptoms and the serum BDNF levels were significantly associated with the mean net scores on the trials in the final two blocks. Based on these results, impaired sensitivity to both reward and punishment is associated with depressive symptoms and reduced serum BDNF levels in chronic schizophrenia patients and may be related to their poor performance on the IGT.

Keywords: brain-derived neurotrophic factor, decision-making, schizophrenia, gambling task, cognition, depression

INTRODUCTION

Brain-derived neurotrophic factor (BDNF), is a member of neurotrophins involved in growth, differentiation, maturation, and survival in immature neurons. In mature neurons, it plays an important role in synaptic plasticity, augmentation of neurotransmission and regulation of receptor sensitivity (Numakawa et al., 2010). BDNF and its high affinity receptor TrkB are widely expressed in developing and adult nervous system, and BDNF is the most abundantly expressed neurotrophic factor in the central nervous system (Balaratnasingam and Janca, 2012). Recent research has provided evidence for the contribution of BDNF to the pathophysiology of schizophrenia. Studies of the BDNF Val66Met (rs6265) showed that the Met allele is associated with lower levels of BDNF secretion and with abnormal hippocampal structure and function, providing evidence for the direct involvement of BDNF in schizophrenia (Egan et al., 2003).

Recent advances in clinical neuroscience indicate that the hippocampus and the orbitofrontal cortex (OFC) play a critical role in complex decision-making processes (Rolls, 1999; Krawczyk, 2002; Johnson et al., 2007; Yu and Fank, 2014). Patients experiencing damage to the hippocampus and the OFC exhibit striking deficits in real-life decision-making, especially social or emotional decision-making, in the context of generally well-preserved intellectual functioning. In addition, growing evidence demonstrates that schizophrenia patients exhibit emotional disturbances and social dysfunction (Mandal et al., 1999; Kohler et al., 2000; Chemerinski et al., 2002), which could be partially explained by impaired decision-making. This impairment in decision-making may occur during interpersonal interactions and social situations (Damasio, 1994). In general, decisions are made based on the assessment of reward and punishment outcomes using both cognitive and affective information (Solms and Turnbull, 2004).

The Iowa Gambling Task (IGT) was developed to assess the role of affective information in decision-making (Bechara et al., 1994). In this task, subjects are presented with four decks of cards and are asked to select any deck in any sequence, and then to take a card from it. The subjects win or lose money with each turn of a card. The participants do not appear to understand the contingencies of the game at the onset. Nevertheless, they can quite rapidly develop a "feeling," or "hunch" in the absence of conceptual awareness.

Because cognitive dysfunction is associated with schizophrenia, we hypothesized that the serum BDNF levels are associated with the IGT scores of the chronic schizophrenia patients.

MATERIALS AND METHODS

SUBJECTS

Eighty-six chronic schizophrenia outpatients recruited from the University of Occupational and Environmental Health participated in the present study and met the following inclusion

criteria: (1) aged 20–60 years; (2) chronic illness without acute exacerbation; and (3) continuously receiving a stable dose of antipsychotics for at least 3 months. The exclusion criteria were: (1) any comorbid central nervous system disorder; (2) severe psychotic symptoms; (3) meeting the DSM-IV criteria for alcohol or other substance dependence; (4) meeting the DSM-IV criteria for mental retardation; (5) receiving antidepressants; (6) treatment with electroconvulsive therapy in the 6 months preceding the study; (7) receiving clozapine; and (8) inability to understand the study protocol. The diagnosis of schizophrenia was established based on the Structured Clinical Interview for DMS-IV (SCID) (First et al., 1996) and a comprehensive review of the patients' medical records. All patients met the criteria for schizophrenia. None were comorbid with any other psychiatric disorders. Seventy-eight of the schizophrenia patients were receiving stable dose of one antipsychotic drug (risperidone, olanzapine, quetiapine, aripiprazole, blonanserin, or perospirone). The remaining schizophrenia patients were receiving at least two antipsychotic drugs. Regarding other medications, nine patients were taking stable dosages of mood stabilizer (lithium, valproic acid, or carbamazepine), five were taking stable dosages of anticholinergic drugs and two were taking antidepressant (paroxetine or mirtazapine). Schizophrenic symptoms were rated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

Additionally, we recruited 51 healthy volunteers (26 females and 25 males) for the healthy control group. The healthy controls consisted of individuals matched to the patients with respect to age, gender, and estimated intelligence quotient (IQ). The healthy controls had not experienced a head injury and did not suffer from any neurologic, psychotic, mood, or substance use disorder as evaluated by the SCID.

INTELLIGENCE TEST

The IQ of the participants was estimated using the Japanese Adult Reading Test (Matsuoka et al., 2002; Hori et al., 2008), a Japanese version of the National Adult Reading Test (Nelson and Wilson, 1991), and those individuals exhibiting estimated IQ scores of less than 80 were excluded from this study.

IGT

Decision-making ability was assessed using the computerized version of the IGT in Japanese (Bechara et al., 1994, 1999, 2005). Decks of cards labeled "A," "B," "C," or "D" were placed in front of the subjects from left to right. Initially, 200,000 yen were given to each subject. The subjects were told that (1) they are to draw one playing card from one of the four decks on each turn, (2) this game involves betting across multiple turns, (3) they receive money every time that they draw a card but that a penalty is occasionally applied, and (4) the objective of this game is to maximize the amount of money that they have. When selecting a card, the subjects can draw a card from any of the decks and can change their selection any time as many times as they choose. The game ended at the 100th draw of a card by a subject, but the subjects were not informed about this rule beforehand. The subjects received a reward each time they drew a card; if they selected a card from the deck A or B, a reward of 10,000 yen was applied, and if they selected a card from the deck C or D, a reward of 5000 yen was applied. Simultaneously, a penalty is applied; decks A and B are referred to as "bad decks" because the immediate reward at the time of the draw is high but the penalty is also high and frequent; therefore, the player ultimately loses money as cards are drawn from these decks. Alternatively, decks C and D are referred to as the "good decks" because the immediate reward is low but the frequency and amount of the penalty is low; therefore, players who draw cards from these decks ultimately earn money. Additionally, decks A and C are categorized as "low magnitude decks" in which a low penalty is applied at a relatively high frequency, whereas decks B and D are categorized as "high magnitude decks" in which a high penalty is applied at a relatively low frequency. The task ended after 100 selections. Neither the risks of rewards or penalties for each deck nor the number of selections allowed was disclosed to the subjects. The composition of the final score and the total amount of money held by each subject at the end of the task was not disclosed to the subjects. This score represented the extent to which socially valuable resources had been increased and may also indicate the amount of risk that the subject was willing to accept given that they may have continued to lose. The frequency of shifting between advantageous (C and D) and disadvantageous (A and B) decks by the subject was computed for every 20 cards, for a total of 5 blocks.

This examination is an exercise in which the subjects are rewarded as well as occasionally penalized with each draw of a card. The subjects can learn the types of rewards and penalties that are applied and can evaluate and change their selections during the process of the game. In this examination, the subjects must use cognitive processing to predict outcomes associated with their selection of cards and generate future predictions using a complex set of results and repeated decisions.

BDNF MEASUREMENT

All blood samples were obtained between 7:00 and 10:00 a.m. in the morning fasting. Fifteen milliliters of venous blood was drawn with subjects in the supine position, after the subjects had been lying at rest overnight.

The serum BDNF levels were measured using a BDNF Emax Immunoassay Kit (Promega, Madison, WI, USA) according to the manufacturer's instructions. In short, 96-well microplates were coated with an anti-BDNF monoclonal antibody and incubated at 4°C for 18 h. The plates were incubated in a blocking buffer for 1 h at room temperature. The samples were diluted 100 times with assay buffer, and BDNF standards were maintained at room temperature under horizontal shaking for 2 h, followed by washing with the appropriate washing buffer. The plates were incubated with anti-human BDNF polyclonal antibody at room temperature for 2 h and washed with the washing buffer. Then, the plates were incubated in an anti-IgY antibody conjugated to horseradish peroxidase for 1 h at room temperature, followed by incubation in peroxidase substrate and a tetramethylbenzidine solution to induce a colorized reaction. This reaction was stopped using 1 mol/L hydrochloric acid. The absorbance at 450 nm was measured using an Emax automated microplate reader. The measurements were performed in duplicate. The standard curve was linear from 5 to 5000 pg/mL, and the detection limit was 10 pg/mL. The intra- and inter-assay coefficients of variation were 5 and 7%,

respectively. The recovery rate of exogenously added BDNF to the measured plasma samples was more than 95%.

Written informed consent was obtained from all of the subjects who participated in this study. The study protocols were approved by the Ethics Committee of the University of Occupational and Environmental Health and included standard procedures for clinical research involving vulnerable participants in Japan. This study was performed according to the ethical standards of the Declaration of Helsinki. If a participant exhibited a compromised ability to consent, we excluded this individual from this study. All participants who declined to participate or otherwise did not participate were eligible for treatment and were not disadvantaged in any other manner because of their lack of participation in this study.

STATISTICAL ANALYSIS

The differences in the clinical variables between the groups were assessed using the *t*-test and the χ^2 test for parametric data or using the Mann–Whitney *U*-test and the Fisher exact test for non-parametric variables. Data analysis of the IGT outcome variables was conducted using *t*-tests and repeated-measures analysis of variance. A multiple linear regression was employed to analyze the effect of the serum BDNF levels on the IGT scores while adjusting for confounding factors [depression score on the PANSS, age, estimated IQ, Chlorpromazine-equivalent (CPZ-eq), and PANSS-T score]. The correlations between the PANSS scores, the IGT scores, and the serum BDNF levels were evaluated using Pearson's correlation analysis. *P*-values of <0.05 were considered to be significant. The data were analyzed using stata13.1 software for Windows.

RESULTS

The demographic characteristics of the subjects are summarized in **Table 1**. No significant differences in age, gender, estimated IQ, or the serum BDNF levels were detected between the two groups.

GAMBLING TASK PERFORMANCE

Descriptive data for the performance on the IGT are presented in **Table 2**. The schizophrenia patients displayed significantly smaller difference scores on the advantageous minus disadvantageous deck selection index and earned significantly less money than the controls.

The learning curves of each group are shown in **Figure 1**. There were significant main effects of the group ($p < 0.001$) and the block ($p < 0.001$) and a significant group × block interaction ($p < 0.001$). A follow-up independent *t*-test indicated that the controls performed better than the schizophrenia patients during the final three blocks but not during the first two blocks. Even after correction for multiple comparisons, this between-group difference remained statistically significant for the final three blocks.

The between-group differences in selections from each deck were examined using a 2 (group) × 4 (deck) repeated-measures ANOVA. There was a significant main effect of the deck ($p < 0.001$) and a significant group × deck interaction ($p < 0.001$). Follow-up *t*-tests evaluated the between-group differences in the selection from each deck. As shown in **Figure 2**, the schizophrenia patients selected deck B more frequently and deck C less frequently than the controls, whereas the two groups did not differ in the selection of decks A and D ($p < 0.05$, even after the Bonferroni correction). Within-group comparisons were used to clarify the pattern of performance; the controls selected the advantageous decks more frequently [(C + D) − (A + B)], ($t = 3.95$, $p < 0.001$) than the patients with schizophrenia.

Table 1 | Demographic and clinical information of the schizophrenia patients and the healthy control group.

	Healthy control	Schizophrenia group	*p*-value
Age (year)	36.7 ± 9.9	35.1 ± 12.1	0.43
Gender (M/F)	25/26	43/43	0.91
Education (years)	13.4 ± 2.2	12.7 ± 2.7	0.15
Estimated IQ	101.8 ± 7.6	99.4 ± 8.2	0.09
Duration of the illness (years)		11.4 ± 13.2	
SCHIZOPHRENIA DIAGNOSIS			
Paranoid type		47	
Disorganized type		27	
Catatonic type		5	
Indifferenciated type		7	
PANSS-P		17.2 ± 4.7	
PANSS-N		20.4 ± 4.6	
PANSS-G		33.2 ± 7.0	
PANSS-T		70.7 ± 11.7	
CPZeq of total antipsychotic drugs(mg/day)		470.1 ± 293.0	
Serum BDNF(ng/ml)	14.1 ± 7.3	11.8 ± 7.0	0.06

PANSS-P, PANSS positive score; PANSS-N, PANSS negative score; PANSS-G, PANSS general psychopathological score; PANSS-T, PANSS total score; CPZ-eq, chlorpromazine-equivalent.

GAMBLING TASK PERFORMANCE, CLINICAL SYMPTOMS, AND SERUM BDNF LEVELS

No correlation was found between the total scores and mean net scores on the IGT and the PANSS-P, PANSS-N, or PANSS-T (**Table 3**). A significant negative correlation was detected between the mean net scores on trials 61–100 and the PANSS-G scores. A significant negative correlation was observed between the mean net scores on the trials in the final two blocks (61–80 and 81–100) and the serum BDNF levels (**Table 3**). **Table 4** shows the multiple regression analysis results for the mean net scores on each block of the trials. Depressive symptoms and the serum BDNF levels were significantly associated with the mean net scores on the trials in the final two blocks.

DISCUSSION

A significant finding in the present study was that the serum BDNF levels and depressive symptoms correlated with decision-making. Several previous studies reported that schizophrenia patients exhibited diminished decision-making abilities compared to healthy individuals (Beninger et al., 2003; Ritter et al., 2004; Lee et al., 2007; Kim et al., 2009; Struglia et al., 2011). To the best of our knowledge, this is the first report to provide

Table 2 | Iowa Gambling Task performance of the schizophrenia patients and the healthy control group.

	Healthy control	Schizophrenia	*t*	*df*	*p*
Mean amount of money earned (yen)	219902.0 ± 72770.1	162348.8 ± 72369.9	4.48	135	< 0.001
No. of cards chosen from deck A	17.7 ± 6.9	18.6 ± 6.0	−0.75	135	0.44
No. of cards chosen from deck B	26.0 ± 12.2	34.5 ± 11.1	−4.1	135	< 0.001
No. of cards chosen from deck C	30.7 ± 12.6	19.6 ± 6.1	5.89	135	< 0.001
No. of cards chosen from deck D	25.2 ± 8.9	27.2 ± 9.0	−1.21	135	0.23
Choice advantageous minus disadvantageous decks	12.2 ± 32.6	−6.3 ± 22.3	−3.6	135	< 0.001

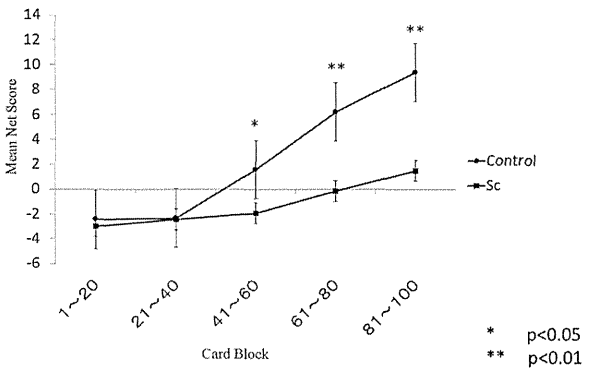

FIGURE 1 | Iowa Gambling Task in schizophrenia and healthy subjects.

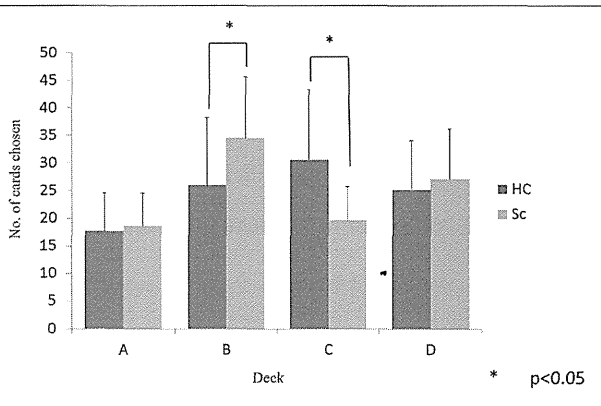

FIGURE 2 | Number of card choice selected from each deck during the 100-card task.

evidence suggesting that the serum BDNF levels reflect decision-making ability in patients with chronic schizophrenia. A recent meta-analysis revealed that the serum BDNF levels in schizophrenia patients are lower than those in healthy individuals (Green et al., 2011). In addition, recent studies have reported an association between poor performance on the IGT and the volume of several lesions in the hippocampus (Bonatti et al., 2009; Labudda et al., 2009; Yamano et al., 2011). The expression level of BDNF is normally high in the hippocampus. Taking these findings into account, diminished serum BDNF level in schizophrenia patients may reflect their poor decision-making performance. In short, serum BDNF may serve as a biomarker of decision-making ability in schizophrenia patients.

Wilder et al. reported that schizophrenia patients often selected the decks corresponding to infrequent and high-magnitude punishments (Wilder et al., 1998). Another study confirmed the finding that schizophrenia patients performed poorly compared to healthy individuals and often selected cards from the deck corresponding to high-magnitude punishments (Shurman et al., 2005). In the present study, the schizophrenia patients selected from good decks during the latter half of the task; however, optimizing the selection pattern appeared to be more difficult for the schizophrenia patients compared to the healthy individuals. Therefore, schizophrenia patients may tend to perform the same pattern of changes in the selection of the decks on the IGT as the control subjects. The magnitude of the occasional penalties has been reported to have little impact on the pattern of card selection.

The results in the present study are in accordance with those of previous publications (Beninger et al., 2003; Ritter et al., 2004; Shurman et al., 2005; Lee et al., 2007; Kim et al., 2009; Struglia et al., 2011). In addition, the present study revealed a significant correlation between decision-making performance and certain psychiatric symptoms. Previous studies have reported inconsistent results regarding the relationship between the IGT score and symptoms of schizophrenia, including a significant correlation to not only negative symptoms of schizophrenia (Shurman et al., 2005) but also positive symptoms of schizophrenia (Struglia et al., 2011). Several studies demonstrated an association between the serum BDNF levels and severity of major depressive disorder (Shimizu et al., 2003; Dell'Osso et al., 2010; Kurita et al., 2012; Yoshiumra et al., 2012). In contrast, no correlations existed between the serum BDNF levels and severity of depression (Karege et al., 2002b; Piccinni et al., 2008; Park et al., 2014). Taken together, it remains controversial that severity of a depressive state influences decision-making in schizophrenia patients. In short, it is not elucidated whether serum BDNF levels reflect or not depressive factors in schizophrenia. One study reported that depressive symptoms are associated with QOL in schizophrenia (Ueoka et al., 2011). Therefore, treatment targeting depressive symptoms may improve the QOL in schizophrenia patients.

The present study contained several limitations. First, the patients with schizophrenia were not classified into subtypes. Second, the schizophrenia patients were receiving various antipsychotic medications when the IGT was performed. Third, the number of subjects in the control group was small. Fourth, the schizophrenia patient group was receiving antipsychotics, a

Table 3 | Correlation between the Iowa Gambling Task performance and serum BDNF, estimated IQ, and clinical symptoms.

	Mean amount of money earned (yen)	1~20	21~40	41~60	61~80	81~100
Serum BDNF concentration (ng/ml)	0.06	0.02	0.03	0.09	0.24*	0.24*
CPZeq of total antipsychotic drugs(mg/day)	0.06	−0.05	−0.09	0.00	−0.1	−0.07
Estimate IQ	0.02	−0.06	−0.04	−0.01	−0.03	−0.06
PANSS-P	0.08	0.02	−0.08	0.00	0.02	0.02
PANSS-N	0.07	−0.03	−0.02	−0.1	−0.08	−0.02
PANSS-G	0.04	−0.03	−0.07	−0.01	−0.25*	−0.23*
PANSS-T	0.08	−0.01	−0.08	−0.04	−0.17	−0.13

CPZ-eq, chlorpromazine-equivalent.
*$p < 0.05$.

Table 4 | Multiple regression analysis results for the mean net scores on each block of the trials.

	Independent variables	Multiple regression statistic			
		β	***SE***	***t*-value**	***p*-value**
IGT-1	Age	0.019	0.045	0.43	0.667
	CPZ-eq	−0.001	0.001	−0.62	0.535
	Depression	1.252	0.869	1.44	0.153
	PANSS-T	−0.459	0.051	−0.91	0.367
	Estimated-IQ	−0.399	0.060	−0.67	0.506
	Serum BDNF levels	0.009	0.070	0.13	0.894
IGT-2	Age	−0.050	0.054	−0.93	0.354
	CPZ-eq	−0.000	0.002	−0.21	0.831
	Depression	0.518	1.041	0.50	0.620
	PANSS-T	−0.049	0.06	−0.80	0.424
	Estimated-IQ	−0.039	0.071	−0.55	0.584
	Serum BDNF levels	0.019	0.084	0.23	0.819
IGT-3	Age	−0.117	0.056	−2.07	0.042*
	CPZ-eq	0.002	0.002	1.02	0.313
	Depression	0.834	1.084	0.77	0.444
	PANSS-T	−0.040	0.063	−0.63	0.532
	Estimated-IQ	−0.028	0.075	−0.37	0.710
	Serum BDNF levels	0.078	0.088	0.89	0.378
IGT-4	Age	−0.054	0.071	−0.75	0.453
	CPZ-eq	−0.000	0.002	−0.10	0.919
	Depression	−3.502	1.376	−2.54	0.013*
	PANSS-T	0.034	0.080	0.42	0.673
	Estimated-IQ	−0.017	0.095	−0.18	0.857
	Serum BDNF levels	0.23	0.112	2.06	0.043*
IGT-5	Age	−0.674	0.084	−0.81	0.423
	CPZ-eq	0.000	0.003	0.09	0.929
	Depression	−4.686	1.619	−2.89	0.005*
	PANSS-T	0.077	0.094	0.82	0.414
	Estimated-IQ	−0.458	0.111	−0.41	0.682
	Serum BDNF levels	0.269	0.131	2.05	0.044*

PANSS-T, PANSS total score; CPZ-eq, chlorpromazine-equivalent; IGT-1: Card block 1-20; IGT-2: Card block 21-40; IGT-3: Card block 41-60; IGT-4: Card block 61-80; IGT-5: Card block 81-100.
*$p < 0.05$.

relevant problem because of the influence of the drugs on the BDNF levels. Fifth, since we evaluated the depressive symptoms in schizophrenia with only PANSS depressive items, we were poorly assessed and insufficient. Last, there is increasing evidence that sampling characteristics, several sociodemographic variables (such as age, sex, urbanicity, BMI), life-style factors (such as food, alcohol intake, and smoking status), somatic disease, and even self-reported depressive symptoms are relevant determinants of serum BDNF levels (Radka et al., 1996; Karege et al., 2002a; Bus et al., 2011). In conclusion, both depressive symptoms and the serum BDNF levels may be associated with the impairment of decision-making in schizophrenia patients.

AUTHOR CONTRIBUTIONS

Dr. Hikaru Hori designed the study, performed the cognitive battery, collected the clinical data, performed the statistical analyses, wrote the first draft of the manuscript, and performed literature searches. Dr. Reiji Yoshimura and Dr. Jun Nakamura developed the study protocol and wrote the final manuscript. Dr. Asuka Katsuki performed the cognitive battery. Dr. Kiyokazu Atake collected the clinical data. All authors contributed to and approved the final manuscript.

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REFERENCES

Balaratnasingam, S., and Janca, A. (2012). Brain derived neurotrophic factor. A novel neurotrophin involved in psychiatric and neurological disorders. *Pharmacol. Ther.* 134, 116–124. doi: 10.1016/j.pharmthera.2012.01.006

Bechara, A., Damashio, H., Damasio, A. R., and Lee, G. P. (1999). Different contributions of the human amygdale and ventromedial prefrontal cortex to decision-making. *J. Neurosci.* 19, 5473–5481.

Bechara, A., Damashio, H., Tranel, D., and Damasio, A. R. (2005). The Iowa Gambling Task and somatic marker hypothsis: some questions and answers. *Trends Cogn. Sci.* 985, 356–369. doi: 10.1016/j.tics.2005.02.002

Bechara, A., Damasio, A. R., Damasio, H., and Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 50, 7–15. doi: 10.1016/0010-0277(94)90018-3

Beninger, R. J., Wasserman, J., Zanibbi, K., Charbonneau, D., Mangels, J., and Beninger, B. V. (2003). Typical and atypical antipsychotic medications differentially affect two nondeclarative memory tasks in schizophrenic patients: a double dissociation. *Schizophr. Res.* 61, 281–292. doi: 10.1016/S0920-9964(02)00315-8

Bonatti, E., Kuchukhidze, G., Zamarian, L., Trinka, E., Bodner, T., Benke, T., et al. (2009). Decision making in ambiguous and risky situations after unilateral temporal lobe epilepsy surgery. *Epilepsy Behav.* 14, 665–673. doi: 10.1016/j.yebeh.2009.02.015

Bus, B. A., Molendijk, M. L., Penninx, B. J., Buitelaar, J. K., Kenis, G., Prickaerts, J., et al. (2011). Determinations of serum brain-derived neurotrophic factor. *Psychoendocrinology* 36, 228–239. doi: 10.1016/j.psyneuen.2010.07.013

Chemerinski, E., Nopoulos, P. C., Crespo-Facorro, B., Andreasen, N., and Magnotta, V. (2002). Morphology of the ventral frontal cortex in schizophrenia: relationship with social dysfunction. *Biol. Psychiatry* 52, 1–8. doi: 10.1016/S0006-3223(01)01363-4

Damasio, A. R. (1994). *Emotion, Reason and the Human Brain.* New York, NY: Agrosset/Putnam Book.

Dell'Osso, L., Del, Debbio, A., Veltri, A., Bianchi, C., Roncaglia, I., Carlini, M., et al. (2010). Associations between brain-derived neurotrophic factor plasma levels and severity of the illness, recurrence and symptoms in depressed patients. *Neuropsychobiology* 62, 207–212. doi: 10.1159/000319946

Egan, M. F., Weinberger, D. R., and Lu, B. (2003). Schizophrenia, III: brain-derived neurotrophic factor and genetic risk. *Am. J. Psychiatry* 160:1242. doi: 10.1176/appi.ajp.160.7.1242

First, M. B., Gibbons, M., Spitzer, R. L., and Williams, B. W. (1996). *Users Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders-Research Version-(SCID- I, Version 2.0, February 1996 Final Version).* New York, NY: Biometric Research Department.

Green, M. J., Matheson, S. L., Shephered, A., Weickert, C. S., and Carr, V. J. (2011). Brain-derived neurotrophic factor levels in schizophrenia: s systematic review with meta-analysis. *Mol. Psychiatry* 16, 960–972. doi: 10.1038/mp.2010.88

Hori, H., Noguchi, H., Hashimoto, R., Okabe, S., Saitoh, O., and Kunugi, H. (2008). IQ decline and memory impairment in Japanese patients with chronic schizophrenia. *Psychiatry Res.* 158, 251–255. doi: 10.1016/j.psychres.2007.11.002

Johnson, A., van der Meer, M. A., and Redish, A. D. (2007). Integrating hippocampus and striatum in decision-making. *Curr. Opin. Neurobiol.* 17, 692–697. doi: 10.1016/j.conb.2008.01.003

Karege, F., Perret, G., Bondolfi, G., Schwald, M., Bertschy, G., and Aubry, J. M. (2002a). Decreased serum brain-derived neurotrophic factor levels in major depressed patients. *Psychiatry Res.* 109, 143–148. doi: 10.1016/S0165-1781(02)00005-7

Karege, F., Schwald, M., and Cisse, M. (2002b). Postnatal developmental profile of brain-derived neurotrophic factor in rat brain and platelets. *Neurosci. Lett.* 328, 261–264. doi: 10.1016/S0304-3940(02)00529-3

Kay, S. R., Opler, L. A., and Fiszbein, A. (1987). Positive and Negative Syndrome Scale (PANSS) manual. *Schizophr. Bull.* 13, 261–276. doi: 10.1093/schbul/13.2.261

Kim, T. Y., Lee, K. Y., and Lee, S. J. (2009). Deficit in decision-making in chronic, stable schizophrenia: from a reward and punishment perspective. *Psychiatry Investig.* 6, 26–33. doi: 10.4306/pi.2009.6.1.26

Kohler, C. G., Bilker, W., Hagendoorn, M., Gur, R. E., and Gur, R. C. (2000). Emotion recognition deficit in schizophrenia: association with symptomatology and cognition. *Biol. Psychiatry* 48, 127–136. doi: 10.1016/S0006-3223(00)00847-7

Krawczyk, D. C. (2002). Contributions of the prefrontal cortex to the neural basis of human decision making. *Neurosci. Biobehav. Rev.* 26, 631–664. doi: 10.1016/S0149-7634(02)00021-0

Kurita, M., Nishino, S., Kato, M., Numata, Y., and Sato, T. (2012). Plasma brain-derived neurotrophic factor levels predict the clinical outcome of depression treatment in a naturalistic study. *PLoS ONE* 7:e39212 doi: 10.1371/journal.pone.0039212

Labudda, K., Frigge, K., Horstmann, S., Agngenendt, J., Woermann, F. G., Ebner, A., et al. (2009). Decision making in patients with temporal lobe epilepsy. *Neuropsychologia* 47, 50–58. doi: 10.1016/j.neuropsychologia.2008.08.014

Lee, Y., Kim, Y. T., Seo, E., Park, O., Jeong, S. H., Kim, S. H., et al. (2007). Dissociation of emotional decision-making from cognitive decision-making in chronic schizophrenia. *Psychiatry Res.* 152, 113–120. doi: 10.1016/j.psychres.2006.02.001

Mandal, M. K., Jain, A., Haque-Nizamie, S., Weiss, U., and Schneider, F. (1999). Generality and specificity of emotion-recognition deficit in schizophrenic patients with positive and negative symptoms. *Psychiatry Res.* 87, 39–46. doi: 10.1016/S0165-1781(99)00047-5

Matsuoka, K., Kim, Y., Hiro, H., Miyamoto, Y., Fujita, K., Tanaka, K., et al. (2002). Development of Japanese Adult Reading Test (JART) for predicting premorbid IQ in mild dementia. *Clin. Psychiatry* 44, 503–511 (in Japanese).

Nelson, H. E., and Wilson, J. R. (1991). *National Adult Reading Test (NART), 2nd Edn.* Windsor: NFER-NELSON

Numakawa, T., Suzuki, S., Kumamaru, E., Adachi, N., Richards, M., and Kunugi, H. (2010). BDNF function and intracellular signalling in neurons. *Histol. Histopathol.* 25, 237–258.

Park, Y. M., Lee, B. H., Um, T. H., and Kim, S. (2014). Serum BDNF levels in relation to illness severity, suicide attempts, and central serotonin activity in patients with major depressive disorder: a pilot study. *PLoS ONE* 9:e91061. doi: 10.1371/journal.pone.0091061

Piccinni, A., Marazziti, D., Catena, M., Domenici, L., Del Debbio, A., Bianchi, C., et al. (2008). Plasma and serum brain-derived neurotrophic factor (BDNF) in depressed patients during 1 year of antidepressant treatments. *J. Affect. Disord.* 105, 279–283. doi: 10.1016/j.jad.2007.05.005

Radka, S. F., Holst, P. A., Frische, M., and Alter, C. A. (1996). Presence of brain-derived neurotrophic factor in brain and human and rat but not mouse serum detected by sensitive and specific immunoassay. *Brain Res.* 709, 122–301. doi: 10.1016/0006-8993(95)01321-0

Ritter, L. M., Meador-Woodruff, J. H., and Dalack, G. W. (2004). Neurocognitive measures of prefrontal cortical dysfunction in schizophrenia. *Schizophr. Res.* 68, 65–73. doi: 10.1016/S0920-9964(03)00086-0

Rolls, E. T. (1999). *The Brain and Emotion*. Oxford: Oxford University Press.

Shimizu, E., Hashimoto, K., Okamura, N., Koike, K., Komatsu, N., Kumakiri, C., et al. (2003). Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. *Biol. Psychiatry* 54, 70–75. doi: 10.1016/S0006-3223(03)00181-1

Shurman, B., Horan, W. P., and Nuechterlein, K. H. (2005). Schizophrenia patients demonstrate a distinctive pattern of decision-making impairment on the Iowa Gambling Task. *Schizophr. Res.* 72, 215–224. doi: 10.1016/j.schres.2004.03.020

Solms, M., and Turnbull, O. (2004). *The Brain and the Inner World: an Introduction to the Neuroscience of Subjective Experience*. New York, NY: Other Press.

Struglia, F., Stratta, P., Gianfelice, D., Pacifico, R., Riccardi, I., Rossi, A., et al. (2011). Decision-making impairment in schizophrenia: relationships with positive symptomatology. *Neurosci. Lett.* 502, 80–83. doi: 10.1016/j.neulet.2011.07.017

Ueoka, Y., Tomotake, M., Tanaka, T., Kaneda, Y., Taniguchi, K., Nakatani, M., et al. (2011). Quality of life and cognitive dysfunction in people with schizophrenia. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 35, 53–59. doi: 10.1016/j.pnpbp.2010.08.018

Wilder, K. E., Weinberger, D., and Goldberg, T. E. (1998). Operant conditioning and the orbitofrontal cortex in schizophrenic patients: unexpected evidence for intact functioning. *Schizophr. Res.* 30, 169–174. doi: 10.1016/S0920-9964(97)00135-7

Yamano, M., Akamatsu, N., Tsuji, S., Kobayakawa, M., and Kawamura, M. (2011). Decision-making in temporal lobe epilepsy examined with the Iowa gambling task. *Epilepsy Res.* 93, 33–38. doi: 10.1016/j.eplepsyres.2010.10.009

Yoshiumra, R., Kishi, T., Suzuki, A., Umene-Nakano, W., Ikenouchi-Sugita, A., Hori, H., et al. (2012). The brain-derived neurotrophic factor (BDNF) polymorphism Val66Met is associated with neither serum BDNF level nor response to selective serotonin reuptake inhibitors in depressed Japanese patients. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 35, 1022–1025. doi: 10.1016/j.pnpbp.2011.02.009

Yu, J. Y., and Fank, L. M. (2014). Hippocampal-cortical interaction in decision-making. *Neurobiol. Learn. Mem.* doi: 10.1016/j.nlm.2014.02.002. [Epub ahead of print].

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ORIGINAL RESEARCH

Effect of blonanserin on cognitive and social function in acute phase Japanese schizophrenia compared with risperidone

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Background: This study aims to determine the effectiveness of blonanserin (BNS) on the cognitive and social functions of patients with schizophrenia compared with risperidone (RIS) during acute-phase (8-week) treatment.

Methods: A total of 39 schizophrenia inpatients were included in this study. The subjects received either BNS (N=20) or RIS (N=19), and the clinical responses were evaluated periodically. The concomitant use of mood stabilizers was not allowed. Efficacy was assessed with the Positive and Negative Syndrome Scale for schizophrenia. Cognition was assessed using the Brief Assessment of Cognition in Schizophrenia, Japanese-language version. Social function was assessed using the Life Assessment Scale for the Mentally Ill.

Results: For both groups, each assessment exhibited a decrease in the mean change from baseline on the Positive and Negative Syndrome Scale. The depression subscale was significantly improved in the BNS group compared with the RIS group at 8 weeks after administration. BNS improved verbal fluency and executive function (cognitive function) and daily living and work skills (social function). Compared with the RIS group, BNS was observed to improve daily living.

Conclusion: BNS may improve psychotic symptoms, cognitive function, and daily living in patients with acute-phase schizophrenia. BNS may be superior to RIS in the improvement of daily living.

Keywords: risperidone, blonanserin, schizophrenia, cognitive function, social function, acute-phase

Introduction

Cognitive improvements in patients with schizophrenia are strongly associated with quality of life and independent living, whereas the successful treatment of positive symptoms has not been demonstrated to significantly improve employment status or social relationships.[1] A number of studies have claimed cognitive benefits from treatment with various atypical antipsychotics; however, the pattern and degree of cognitive improvement differ from drug to drug.[2–6] The study of social cognition in schizophrenia has increased rapidly during the past decade. Schizophrenia patients exhibit impairments in both low- and high-level social cognitive processes,[7–10] and their impaired social cognition is consistently related to functional outcome.[11,12]

Blonanserin (BNS) was developed in Japan as a novel antipsychotic drug,[13,14] and it was approved for the treatment of schizophrenia in Japan and Korea.[15] BNS has a high affinity for the dopamine $D_{2,3}$ and serotonin 5-HT_{2A} receptors, but low affinity for the $D_{1,4,5}$, adrenergic $\alpha_{1,2}$, β, 5-HT_{1A}, $5HT_{2B}$, $5HT_{2C}$, $5HT_{3-7}$, histamine H_1, and muscarinic M_1 receptors.[14,15] A preclinical study demonstrated that BNS increased

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the extracellular levels of dopamine and norepinephrine in the prefrontal cortex.[16] In a recent meta-analysis, the effect of BNS was demonstrated to be equal to that of haloperidol and risperidone (RIS) in primary endpoints and superior to haloperidol in improving negative symptoms in patients with schizophrenia.[17] Moreover, BNS improved verbal fluency and executive function with first-episode schizophrenia.[18] However, to our knowledge, no study has evaluated the effects of BNS on the cognitive and social functions of patients with acute-phase schizophrenia. Furthermore, in the absence of direct comparisons with RIS, it remains difficult to reach a final verdict on the potential additional therapeutic benefits of BNS. Therefore, we examined BNS's effectiveness on cognitive and social function in acute-phase schizophrenia by comparing it with that of RIS.

Methods

Subjects

Thirty-nine inpatients (18 males and 21 females) were included in this study. Twenty were receiving BNS treatment and 19 were receiving RIS treatment as a control group. All of the patients met the diagnostic criteria for schizophrenia based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Test Revision*.[19] Patients with concomitant medical illness (for example, diabetes, high blood pressure, hypothyroidism, or a chronic respiratory condition) were eligible for participating in the study if their condition had been stable for at least 3 months and they had been receiving standard therapy for the condition for at least 1 month.

Patients were excluded for any untreated or unstable clinically significant medical condition, or for any clinically significant laboratory or physical examination abnormality or thyroid function abnormality. A history of seizures, recent drug or alcohol abuse, or any principal psychiatric condition other than schizophrenia were reasons for exclusion, as was a suicide attempt in the current psychotic episode. Patients were excluded if they had received RIS or BNS for the current psychotic episode or electroconvulsive therapy during the previous 6 months. In addition, patients were excluded if they required concomitant therapy with drugs approved for the treatment of memory deficits. Patients who did not tolerate or respond to RIS or BNS during a previous psychotic episode were ineligible. Additionally, patients who had failed more than one adequate trial of antipsychotic treatment for the current psychotic episode were excluded.

All of the subjects who participated in this study were inpatients. Treatment compliance for all of the subjects was confirmed by a nurse.

Study design

Twenty patients were recruited to the present study and assigned to the acute-phase schizophrenia. Patients were administered BNS monotherapy for 8 weeks. The daily doses of the drug were individually adjusted according to the patient's clinical status, and no additional drugs, except lorazepam, were permitted during the study period.

The clinical improvement of the patients was evaluated using the Positive and Negative Syndrome Scale (PANSS)[20] on days 0, 28 (4 weeks), and 56 (8 weeks). Cognitive function and social functions were measured using the Brief Assessment of Cognition in schizophrenia, Japanese language version (BACS-J) and the Life Assessment Scale for the Mentally Ill (LASMI) on days 0 and 56 (8 weeks).

To exclude possible learning effects on BACS-J, 19 patients with acute-phase schizophrenia as a RIS group. The RIS group's dosage and additional drugs were performed on the same conditions as BNS group. The raters were blinded about the treatment status.

Patients with at least a 30% or more decrease in their baseline PANSS scores were defined as responders, whereas those with less than a 30% decrease were regarded as nonresponders. The protocol for this study was approved by the Ethics Committee of the University of Occupational and Environmental Health (Kitakyushu, Fukuoka, Japan). All participants provided their consent to participate after being informed of the study's purpose.

Cognitive functions, social functions, intelligence test, and clinical assessment

The primary outcome measures were the changes in cognitive functions and social functions from baseline to the endpoint. The secondary outcome measures were changes in psychiatric symptoms and the severities of the psychopathologies. The cognitive functions were assessed by trained psychiatrists using the BACS-J.[21] The BACS-J has established reliability and validity and is designed to measure cognitive function in schizophrenia.[21,22] The metric includes brief assessments of verbal memory, working memory, motor speed, verbal fluency, attention and processing speed, and executive function. The primary measures from each BACS-J subtest were standardized by creating *z*-scores (the mean of healthy controls was set to 0, and the standard deviation was set to 1). All of the data from the healthy controls were obtained from a study by Kaneda et al,[23] and a composite score was calculated by averaging all of the *z*-scores for the six primary measures. The influence of age was adjusted using age-matched cohorts of controls

to calculate the BACS-J *z*-scores for each schizophrenia patient in the present study.

We assessed functional outcomes in this study. The LASMI was developed to assess disability in daily life or community functioning,[24–26] and it is one of the most commonly used scales to evaluate community functioning in Japan. The LASMI is composed of the following five categories: 1) daily living; 2) interpersonal relations; 3) work skills; 4) endurance and stability; and 5) self-recognition. Each category consists of several items, with each item being rated on a 5-point scale (responses range from no problem =0 to a serious problem =4). Lower scores indicate higher degrees of independent living in the community. The mean score for each category was calculated by dividing the total score for that category by the number of items. The LASMI scores were assigned based on observations of patient behavior and information from the patients and their families.

Statistical analysis

Differences between the RIS and BNS groups in terms of demographic and baseline characteristics were assessed using independent samples *t*-tests and the chi-square test.

This study's primary aim was to clarify the effects of RIS and BNS on cognitive and social function, as measured by the BACS-J and the LASMI. A repeated measures analysis of covariance was performed for each cognitive and social variable with the baseline data serving as the covariate. For the primary analysis, the between-subjects factor was the group (RIS group and BNS group) and the within-subjects factor was time (day 0 and day 56). The effects of group, time, and group-by-time (interaction effect) were examined. Additionally, we used a Bonferroni correction for multiple comparisons of the BACS-J and LASMI data. In a secondary analysis, within-group improvements in cognitive performance and social function over time were evaluated using paired *t*-tests. All statistical tests were two-tailed, and a *P*-value <0.05 was considered significant. Effect size (Cohen's *d*) was calculated as the within-group differences between the mean values divided by the pooled standard deviation.

Results

A total of 20 patients in the BNS group and 19 patients in the RIS group were recruited and tested at baseline. Of these, 33 patients completed this study (BNS, number [n]=17; RIS, n=16). Baseline demographics or clinical characteristics were comparable between treatment groups (Table 1). During the acute treatment phase, three patients in the BNS group (15.0%) and three patients in the BNS group (15.8%) discontinued their participation prematurely, most of them because of adverse events (Figure 1). Seventeen in the BNS and 16 in the RIS groups were retested on the cognitive measures after 8 weeks. Thus, data from these 17 patients in the BNS group and 16 patients in the RIS group were used for a more complete analysis.

Table 1 Demographic and clinical characteristics of the patient sample at baseline

	RIS group	BNS group	*P*-value
Age (years)	31.1±8.8	29.6±8.3	0.58
Sex (M/F)	9/10	9/11	0.88
Education (years)	13.6±2.4	13.0±2.2	0.40
Handedness (right/left)	19/0	19/1	0.97
Smoking (yes/no)	7/12	8/12	0.84
Duration of illness (years)	7.7±5.7	6.1±4.6	0.33
PANSS			
PANSS-P	29.5±4.1	29.0±6.1	0.76
PANSS-N	29.2±6.9	28.2±7.3	0.66
PANSS-G	47.2±8.6	47.2±7.9	0.99
PANSS-T	105.8±13.8	104.3±14.4	0.73
BACS-J			
Verbal learning	−1.7±0.8	−1.5±0.8	0.44
Working memory	−1.7±0.7	−1.7±0.8	0.86
Motor function	−1.3±0.7	−0.9±0.9	0.20
Verbal fluency	−1.5±0.8	−1.3±0.5	0.32
Attention and processing speed	−1.9±0.5	−1.6±0.4	0.10
Executive function	−1.2±0.5	−1.1±0.6	0.58
LASMI			
Daily living	1.8±0.7	2.0±0.7	0.62
Interpersonal relations	2.1±0.6	2.2±0.6	0.42
Work skills	2.1±0.6	2.3±0.6	0.41
Endurance and stability	3.2±0.9	3.1±1.1	0.78
Self-recognition	2.3±0.8	2.4±0.7	0.82

Abbreviations: RIS, risperidone; BNS, blonanserin; M, male; F, female; PANSS, Positive and Negative Syndrome Scale; P, positive scale score; N, negative scale score; G, general psychopathology subscale score; T, total score; BACS-J, Brief Assessment of Cognition in Schizophrenia, Japanese-language version; LASMI, Life Assessment Scale for the Mentally Ill.

Five patients in the RIS group and 12 in the BNS group used lorazepam for sleep during the trial.

Eight weeks into treatment, the mean (standard deviation) daily doses of RIS and BNS were 3.1 (1.3) mg and 14.6 (4.0) mg, respectively.

Efficacy

Sixteen patients on RIS and 17 on BNS completed the study. Twelve (63.2%) RIS and 12 (60%) BNS patients met the criteria for being responders.

For both groups, each assessment exhibited a decrease in the mean change from baseline on the PANSS (Table 2).

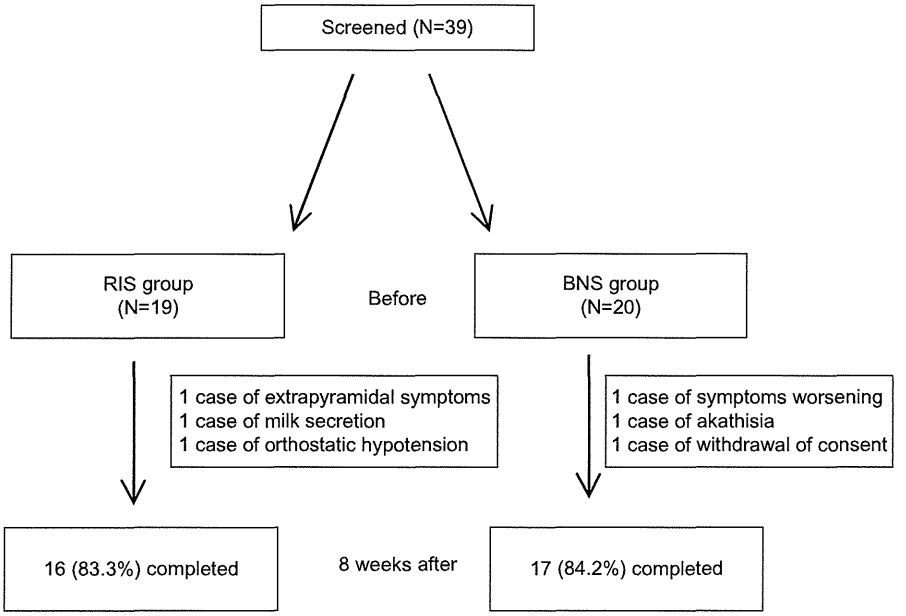

Figure 1 Patient disposition (number of patients who were assigned, treated, and who completed the treatment with the reasons for discontinuation).
Abbreviations: N, number; RIS, risperidone; BNS, blonanserin.

A significantly larger reduction was observed in the RIS group compared to the BNS group for changes in the scores on two PANSS items: the excitement and hostility scores at 4 weeks. However, these significant differences were not observed at 8 weeks. That is, the BNS group displayed a faster decrease in mean PANSS depression scores ($P<0.05$ for week 8).

Table 2 PANSS score changes for the risperidone and blonanserin groups

	Risperidone		Blonanserin	
	Mean	**SD**	**Mean**	**SD**
PANSS positive subscale score				
Baseline	29.5	4.1	29.0	6.1
4 weeks	22.0	5.6*	21.8	6.4*
8 weeks	19.4	7.2*	19.5	8.1*
PANSS negative subscale score				
Baseline	29.2	6.9	28.2	7.3
4 weeks	27.1	7.2	24.9	7.7
8 weeks	22.7	7.4*	21.4	7.4*
PANSS general psychopathology subscale score				
Baseline	47.2	8.6	47.2	7.9
4 weeks	42.4	9.4	41.7	8.5
8 weeks	38.9	10.6*	38.6	11.2*
PANSS total score				
Baseline	105.8	13.8	104.3	14.4
4 weeks	91.5	16.1*	88.3	15.8*
8 weeks	81.0	22.0*	79.5	23.2*

Note: *$P<0.01$ versus baseline.
Abbreviations: PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

Cognitive function change

Comparisons of the changes in the neurocognitive functions of the treatment groups are summarized in Table 3. No significant differences in the changes were observed in the six BACS-J domains measured.

Paired *t*-tests demonstrated that the *z*-scores for verbal fluency and executive function were significantly improved after treatment with BNS (Table 4), and the *z*-scores for verbal fluency were significantly improved after treatment with RIS (Table 5).

Social function change

Comparisons of the changes in the social functions of the treatment groups are summarized in Table 3. The changes in daily living were significantly larger in the BNS group than in the RIS group. No significant differences between the RIS and BNS groups were observed for the four other domains measured.

Paired *t*-tests demonstrated that the daily living and work skills scores were significantly improved after treatment with BNS (Table 4), and that the work skills scores were significantly improved after treatment with RIS (Table 5).

The relationship between the RIS and BNS doses and the BACS-J scores at 8 weeks

A significant negative correlation was found between RIS dosage and the scores for motor function, attention, and

Table 3 "Time × group" interaction effect on analysis of variance with BACS-J and LASMI data when compared with the BNS group

	F	*P*-value
BACS-J		
Verbal learning	0.10	0.76
Working memory	0.84	0.37
Motor function	1.47	0.23
Verbal fluency	0.03	0.87
Attention and processing speed	0.02	0.90
Executive function	0.40	0.53
LASMI		
Daily living	4.51	0.04
Interpersonal relations	2.77	0.11
Work skills	0.21	0.61
Endurance and stability	0.03	0.87
self recognition	0.01	0.89

Abbreviations: BNS, blonanserin; BACS-J, Brief Assessment of Cognition in Schizophrenia, Japanese-language version; LASMI, Life Assessment Scale for the Mentally Ill.

processing speed at 8 weeks in the RIS group. A significant negative correlation was also found between BNS and the motor function scores (Table 6).

Discussion

In this study, it is noteworthy that BNS has an improving effect on daily living when compared with RIS, although the ameliorating effect on psychiatric symptoms is comparable between the two drugs. Recently, much importance has been attached to the ameliorating effects of antipsychotic drugs, not only on psychiatric symptoms, but also on cognitive and social functions. More notably, it appears that BNS significantly improves social function. Activities of daily living are often habitual and are less influenced by antipsychotic therapy. A previous study showed that there was a positive correlation between improving executive function and improving daily living.[27] Although the precise mechanism behind this effect remains unknown, BNS has been shown to improve daily living by improving executive function. Furthermore, this outcome may be explained by the simple pharmacological profile and lower sedative effect of BNS, although the mechanism underlying the action of BNS has not been fully clarified. Two previous studies reported that RIS has been shown to improve daily living.[28,29] The discrepancy between the studies could be due to differences in the sample, the sample size, or the study periods.

Second, it should be noted that BNS may have a more potent effect on depressive symptoms than RIS in the treatment of patients with acute schizophrenia, whereas RIS manifests its effect on symptoms such as agitation and hostility early after administration. A recent meta-analysis[17] demonstrated that the effect of BNS is equivalent to that of RIS, which was also supported by the present study. When BNS is used in patients who exhibit strong agitation or hostility during the acute phase, the temporary use of concomitant drugs may be beneficial. In fact, when BNS is used during the acute phase, a concomitant drug reportedly increases the drug's continuation rate.[30] However, the effect of RIS on depressive symptoms is poor for the first 8 weeks after administration, and if the patient remains depressed, it may be necessary to consider administering a concomitant drug.

The results of the present study suggest that both RIS and BNS have improving effects on cognitive and social function. Moreover, RIS improved verbal fluency, whereas BNS improved not only verbal fluency, but also executive function. A previous report demonstrated that the improving effect of RIS on verbal fluency is unsatisfactory.[3,31] However,

Table 4 Paired *t*-test results on BACS-J and LASMI data for the BNS group

(N=17)	Baseline	8 weeks later	t	*P*-value	Cohen's d
BACS-J					
Verbal learning	−1.53±0.81	−1.46±0.83	−0.42	0.68	0.09
Working memory	−1.66±0.76	−1.60±0.19	−0.58	0.57	0.09
Motor function	−0.89±0.94	−0.84±0.24	−0.31	0.76	0.05
Verbal fluency	−1.27±0.55	−0.94±0.67	−2.23	0.04	0.56
Attention and processing speed	−1.48±0.50	−1.40±0.59	−0.81	0.42	0.15
Executive function	−1.13±0.57	−0.77±0.69	−2.22	0.04	0.60
LASMI					
Daily living	1.96±0.16	1.77±0.61	2.79	0.01	0.30
Interpersonal relations	2.23±0.61	2.19±0.61	0.21	0.83	0.08
Work skills	2.27±0.62	1.98±0.60	3.61	0.002	0.50
Endurance and stability	3.06±1.12	2.94±1.13	1.07	0.30	0.11
Self-recognition	2.37±0.72	2.25±0.69	0.81	0.43	0.17

Abbreviations: BACS-J, Brief Assessment of Cognition in Schizophrenia, Japanese-language version; LASMI, Life Assessment Scale for the Mentally Ill; BNS, blonanserin; N, number.

Table 5 Paired *t*-test results on BACS-J and LASMI data for the RIS group

(N=16)	Baseline	8 weeks later	t	*P*-value	Cohen's *d*
BACS-J					
Verbal learning	−1.74±0.76	−1.60±0.89	−0.83	0.41	0.18
Working memory	−1.71±0.74	−1.49±0.81	−1.71	0.11	0.29
Motor function	−1.27±0.69	−1.63±0.89	1.18	0.25	0.46
Verbal fluency	−1.48±0.66	−1.18±0.46	−2.81	0.01	0.54
Attention and processing speed	−1.85±0.48	−1.75±0.72	−0.67	0.51	0.17
Executive function	−1.23±0.48	−1.03±0.68	−1.04	0.32	0.36
LASMI					
Daily living	1.84±0.73	1.84±0.64	0.04	0.96	0.003
Interpersonal relations	2.06±0.61	1.94±0.61	2.03	0.06	0.20
Work skills	2.10±0.60	1.86±0.59	3.29	0.005	0.42
Endurance and stability	3.16±0.94	3.06±1.01	1.00	0.33	0.10
self recognition	2.31±0.81	2.16±0.75	1.15	0.27	0.19

Abbreviations: BACS-J, Brief Assessment of Cognition in Schizophrenia, Japanese-language version; LASMI, Life Assessment Scale for the Mentally Ill; RIS, risperidone; N, number.

the present study's results indicated that RIS significantly improved verbal fluency and that the effect size was moderate. BNS exerted improving effects on verbal fluency and executive function, as previously reported.[18] A previous study indicated that the effect size of antipsychotic drugs is small in terms of many variables related to the improvement of cognitive function.[31] However, in this study, this effect was relatively potent. RIS may be effective in improving work skills, whereas BNS may be effective in improving both daily living and work skills. Both drugs appear to improve patients' social lives.

These results suggest that both RIS and BNS are effective in the treatment of schizophrenia. However, the proper use of concomitant drugs may be required, depending on the symptoms that occur during the acute stage. Moreover, both drugs are likely to improve cognitive and social function. BNS may be superior to RIS in the improvement of daily living.

This study had a relatively small sample size, was short-term (8 weeks), and open-label, but it was not double-blind. Therefore, the possibility that bias was introduced to the results cannot be ruled out and, consequently, there are limits to the conclusions that can be drawn from this study. A double-blind, randomized, controlled study on acute schizophrenia may be necessary to clarify the efficacy and safety of RIS and BNS. One must remember that other factors besides antipsychotic drugs, such as the patient's period of illness, preillness intelligence quotient, or cognitive function levels, may influence the present study's results.

In conclusion, RIS and BNS may improve psychotic symptoms, cognitive function, and daily living in patients with acute-phase schizophrenia. BNS may be superior to RIS in the improvement of daily living.

Table 6 The relationship between RIS and BNS doses and BACS-J scores at 8 weeks

	RIS (N=16)	BNS (N=17)
Verbal learning	0.09	0.23
Working memory	0.29	−0.35
Motor function	−0.52*	−0.51*
Verbal fluency	0.05	0.04
Attention and processing speed	−0.50*	0.06
Executive function	0.07	0.20

Note: *$P<0.05$.

Abbreviations: RIS, risperidone; BNS, blonanserin; BACS-J, Brief Assessment of Cognition in Schizophrenia, Japanese-language version; N, number.

Author contributions

Dr Hori designed the study, performed the cognitive battery, collected the clinical data, performed the statistical analyses, wrote the first draft of the manuscript, and managed the literature searches. Dr Yoshimura and Dr Nakamura developed the study protocol and wrote the final manuscript. Dr Katsuki performed the cognitive battery. Dr Yamada, Dr Kamada, and Dr Shibata collected the clinical data. All of the authors took part in either drafting the article or revising it critically for important intellectual content, and approved the final manuscript.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Meltzer HY. Cognitive factors in schizophrenia: causes, impact, and treatment. *CNS Spectr*. 2004;9(10 Suppl 11):15–24.
2. Harvey PD, Meltzer H, Simpson GM, et al. Improvement in cognitive function following a switch to ziprasidone from conventional antipsychotics, olanzapine, or risperidone in outpatients with schizophrenia. *Schizophr Res*. 2004;66(2–3):101–113.

3. Woodward ND, Purdon SE, Meltzer HY, Zald DH. A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. *Int J Neuropsychopharmacol*. 2005;8(3):457–472.
4. Kern RS, Green MF, Cornblatt BA, et al. The neurocognitive effects of aripiprazole: an open-label comparison with olanzapine. *Psychopharmacology (Berl)*. 2006;187(3):312–320.
5. Keefe RS, Sweeney JA, Gu H, et al. Effects of olanzapine, quetiapine, and risperidone on neurocognitive function in early psychosis: a randomized, double-blind 52-week comparison. *Am J Psychiatry*. 2007;164(7):1061–1071.
6. Hori H, Yoshimura R, Katsuki A, et al. The cognitive profile of aripiprazole differs from that of other atypical antipsychotics in schizophrenia patients. *J Psychiatr Res*. 2012;46(6):757–761.
7. Kee KS, Horan WP, Salovey P, et al. Emotional intelligence in schizophrenia. *Schizophr Res*. 2009;107(1):61–68.
8. Kern RS, Green MF, Fiske AP, et al. Theory of mind deficits for processing counterfactual information in persons with chronic schizophrenia. *Psychol Med*. 2009;39(4):645–654.
9. Harvey PO, Lee J, Horan WP, Ochsner K, Green MF. Do patients with schizophrenia benefit from a self-referential memory bias? *Schizophr Res*. 2011;127(1–3):171–177.
10. Lee J, Zaki J, Harvey PO, Ochsner K, Green MF. Schizophrenia patients are impaired in empathic accuracy. *Psychol Med*. 2011;41(11):2297–2304.
11. Fett AK, Viechtbauer W, Dominguez MD, Penn DL, van Os J, Krabbendam L. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. *Neurosci Biobehav Rev*. 2011;35(3):573–588.
12. Horan WP, Green MF, DeGroot M, et al. Social cognition in schizophrenia, Part 2: 12-month stability and prediction of functional outcome in first-episode patients. *Schizophr Bull*. 2012;38(4):865–872.
13. Noda Y, Kurumiya S, Miura Y, Oka M. Comparative study of 2-(4-ethyl-1-piperazinyl)-4-(fluorophenyl)-5,6,7,8,9,10-hexahydrocycloocta[b] pyridine (AD-5423) and haloperidol for their pharmacological activities related to antipsychotic efficacy and/or adverse side-effects. *J Pharmacol Exp Ther*. 1993;265(2):745–751.
14. Oka M, Noda Y, Ochi Y, et al. Pharmacological profile of AD-5423, a novel antipsychotic with both potent dopamine-D2 and serotonin-S2 antagonist properties. *J Pharmacol Exp Ther*. 1993;264(1):158–165.
15. Deeks ED, Keating GM. Blonanserin: a review of its use in the management of schizophrenia. *CNS Drugs*. 2010;24(1):65–84.
16. Ohoyama K, Yamamura S, Hamaguchi T, et al. Effect of novel atypical antipsychotic, blonanserin, on extracellular neurotransmitter level in rat prefrontal cortex. *Eur J Pharmacol*. 2011;653(1–3):47–57.
17. Kishi T, Matsuda Y, Nakamura H, Iwata N. Blonanserin for schizophrenia: systematic review and meta-analysis of double-blind, randomized, controlled trials. *J Psychiatr Res*. 2013;47(2):149–154.
18. Tenjin T, Miyamoto S, Miyake N, et al. Effect of blonanserin on cognitive function in antipsychotic-naïve first-episode schizophrenia. *Hum Psychopharmacol*. 2012;27(1):90–100.
19. American Psychiatric Association. *Diagnostic Criteria from DSM-IV-TR*. Washington, DC: American Psychiatric Association; 2000.
20. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276.
21. Kaneda Y, Sumiyoshi T, Keefe R, Ishimoto Y, Numata S, Ohmori T. Brief assessment of cognition in schizophrenia: validation of the Japanese version. *Psychiatry Clin Neurosci*. 2007;61(6):602–609.
22. Keefe RS, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophr Res*. 2004;68(2–3):283–297.
23. Kaneda Y, Sumiyoshi T, Nakagome K, et al. The brief assessment of cognition in schizophrenia Japanese version (BACS-J). *Seishinigaku*. 2008;50(9):913–917. Japanese.
24. Iwasaki S, Miyauchi M, Oshima I, et al. The development of Life Assessment Scale for the Mentally Ill: an assessment of the reliability. *Seishin Igaku*. 1994;36:1139–1151. Japanese.
25. Iwanami A, Yamashina M, Kazamatsuri H, Kamijima K. P300 and disability of daily life in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 1999;23(3):423–430.
26. Inadomi H, Tanaka G, Watanabe S, et al. Efficacy of 3-year psychiatric daycare treatment in patients with schizophrenia. *Psychiatry Clin Neurosci*. 2005;59(3):246–252.
27. Hori H, Yoshimura R, Katsuki A, Sugita AI, Atake K, Nakamura J. Switching to antipsychotic monotherapy can improve attention and processing speed, and social activity in chronic schizophrenia patients. *J Psychiatr Res*. 2013;47(12):1843–1848.
28. Lieberman RP, Gutkind D, Mintz J, et al. Impact of risperidone versus haloperidol on activities of daily living in the treatment of refractory schizophrenia. *Compr Psychiatry*. 2002;43(6):469–473.
29. Kaneda Y, Ohmori T. Impact of risperidone medication on quality of life and gonadal axis hormones in schizophrenia male patients with acute exacerbation. *Int J Neuropsychopharmacol*. 2003;6(3):247–252.
30. Tsutsumi Y, Kasuga Y, Isaka Y, et al. Effectiveness of blonanserin (BNS) in 70 in-patients with acute phase schizophrenia. *Japanese Journal of Clinical Psychopharmacology*. 2011;14:1523–1540. Japanese.
31. Harvey PD, Keefe RS. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. *Am J Psychiatry*. 2001;158(2):176–184.

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ORIGINAL RESEARCH

Catechol-*O*-methyltransferase Val158Met genotype and the clinical responses to duloxetine treatment or plasma levels of 3-methoxy-4-hydroxyphenylglycol and homovanillic acid in Japanese patients with major depressive disorder

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Purpose: This study investigated the relationships among the plasma levels of catecholamine metabolites, the clinical response to duloxetine treatment, and Val158Met polymorphism of the catechol-*O*-methyltransferase (COMT) gene.

Subjects and methods: Sixty-four patients and 30 healthy control subjects were recruited. Major depressive episodes were diagnosed using the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision criteria. The severity of depression was evaluated using the 17-item Hamilton Rating Scale for Depression (HAMD17). Patients whose HAMD17 scores were 15 or greater were enrolled in the study. Blood sampling and clinical evaluation were performed at week 0 and week 8. The levels of plasma catecholamine metabolites were measured using high-performance liquid chromatography with electrochemical detection. Genotyping was performed using direct sequencing.

Results: Thirty of 45 patients (67%) responded to duloxetine treatment during the 8 weeks of treatment. The baseline plasma levels of 3-methoxy-4-hydroxyphenylglycol (MHPG), but not homovanillic acid (HVA), were lower in patients with major depressive disorder (MDD) who had the Val/Val genotype than in patients who were Met-carriers. Patients with MDD and the Val/Val genotype, but not Met carriers, had increased plasma levels of MHPG after 8 weeks of duloxetine treatment. The baseline plasma MHPG levels in healthy control subjects with the Val/Val genotype were significantly higher than those in patients with MDD. Among the subjects in the MDD group with the Val/Val genotype, the plasma MHPG levels increased to the same degree as in the healthy control subjects with the Val/Val genotype after 8 weeks of duloxetine treatment.

Conclusion: The relationship among the COMT Val158Met polymorphism, plasma levels of catecholamine metabolites, and responses to duloxetine is complex. Nevertheless, our results suggest that patients with MDD and the Val/Val genotype are more sensitive to the influence of noradrenergic neurons by duloxetine treatment.

Keywords: major depressive disorder, duloxetine, catechol-*O*-methyltransferase, 3-methoxy-4-hydroxyphenylglycol, homovanillic acid

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Introduction

Duloxetine, a serotonin–noradrenaline reuptake inhibitor (SNRI), is an effective first-line treatment for patients with major depressive disorder (MDD). Duloxetine is also useful for the treatment of diabetic neuropathic pain and fibromyalgia.[1] Duloxetine

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is generally safe and well tolerated, although it can lead to nausea, headache, dry mouth, insomnia, general fatigue, constipation, diarrhea, dizziness, sweating, sexual dysfunction, and loss of appetite in patients with MDD.[1] We previously reported that milnacipran, another SNRI, increased the plasma levels of 3-methoxy-4-hydroxyphenylglycol (MHPG) (a major metabolite of noradrenaline) in patients with MDD; this increase was related to the milnacipran-associated clinical improvement in patients with MDD.[2] Because duloxetine potently inhibits both serotonin and noradrenaline transporters, we hypothesized that duloxetine (similar to milnacipran) may also increase plasma MHPG levels in patients with MDD. We recently reported that duloxetine treatment for 8 weeks significantly increased MHPG plasma levels in patients with MDD.[3] To the best of our knowledge, this is the first study examining the influence of duloxetine on plasma MHPG levels in patients with MDD. Monoamines play an important role in the pathogenesis of MDD.[4] Our previous studies demonstrated that the response to antidepressants was associated with the plasma levels of catecholamine metabolites.[2,5] Specifically, the plasma levels of catecholamine metabolites, such as MHPG and homovanillic acid (HVA), predicted the response to selective serotonin reuptake inhibitors (SSRIs) and SNRIs.[2,5] Patients with MDD and lower plasma levels of MHPG responded better to milnacipran, and patients with higher plasma levels of MHPG responded better to paroxetine. Considering these findings, an increase in MHPG levels may play an important role in improving depressive symptoms.

Catechol-*O*-methyltransferase (COMT) is a methylation enzyme that participates in the degradation of noradrenaline and dopamine by catalyzing the transfer of a methyl group from *S*-adenosylmethionine. Biochemical studies have established that the enzyme activities of patients with MDD differ from those of non-depressed subjects.[6] The COMT gene is located at 22q 11.21. Val158Met (G324A) (rs 4680), functional polymorphism in the COMT gene, was found to be associated with MDD in a multicenter European study.[7] Furthermore, the valine (Val) allele has been reported to result in three- to fourfold higher COMT activity than the methionine (Met) allele.[8] One recent report suggested an association between the higher activity of the Val/Val-type COMT gene and poor antidepressant treatment response.[9] Furthermore, the Met variants of the COMT gene Val158Met polymorphism was shown to increase the risk of depressed mood and low motivation in Swedish males with MDD.[10]

Considering these findings, we hypothesized that 1) patients with the COMT Val/Val genotype would respond better to duloxetine than COMT Met carriers due to catecholamine deficiencies; 2) patients with the COMT Val/Val genotype would have lower plasma levels of MHPG and HVA than COMT Met carriers; and 3) patients with MDD and the COMT Val/Val genotype would exhibit increased plasma levels of MHPG and HVA compared to COMT Met carriers. To address these hypotheses, we investigated the plasma levels of catecholamine metabolites and the clinical responses to duloxetine treatment in patients with MDD and the COMT Val/Val genotype and in patients with MDD who were COMT Met carriers. To the best of our knowledge, this is the first study to investigate the COMT Val158Met polymorphism, plasma catecholamine metabolite levels, and clinical improvement in response to duloxetine treatment in Japanese patients with MDD.

Subjects

Sixty-four in/outpatients and 30 healthy control subjects were recruited. Major depressive episodes were diagnosed using the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) criteria. Patients whose 17-item Hamilton Rating Scale for Depression (HAMD17) scores were 15 or greater were enrolled in the current study. The exclusion criteria included any history of neurological disease or other physical diseases and comorbidities with other disorders such as bipolar disorder or Axis II disorders (ie, personality disorders or mental retardation diagnosed using the Structured Clinical Interview DSM-IV Axis II instrument). We enrolled 30 sex- and age-matched healthy control subjects without any psychiatric disorders (diagnosed by KA using the Structured Clinical Interview for DSM-IV Axis I Disorders, Non-patient Edition [SCID-I/NP]). All of the subjects were provided with information about the procedures. Written informed consent was obtained via forms approved by the local Ethics Committee of the University of Occupational and Environmental Health, Kitakyushu, Japan.

Methods

The present study utilized an open-label and non-fixed dose design. All of the patients were administered duloxetine monotherapy for 8 weeks. Benzodiazepines were used, if necessary, during the treatment period. A 1-week washout period occurred before duloxetine treatment began. The severity of depressive symptoms was evaluated (by KA) each week using the HAMD17. We defined responders as patients whose HAMD17 scores decreased by 50% or more. Blood sampling and clinical evaluations were performed at

Table 1 The demographic data for the patients with major depressive disorder and the healthy control subjects

	Patients (N=45)	Controls (N=30)	*P*-value
Age (years)	50.6± 15.3	46.5±10.6	0.251*
Sex (male/female) (n)	23/22	14/16	0.706**

Notes: *P*-values calculated using *Student's *t*-test, **χ^2 test. Age is presented as mean ± standard deviation.

week 0 and week 8. Forty-five of the 64 patients (70%) finished the study. The demographic data of the subjects who finished the study are shown in Table 1. The persistence rate is illustrated in Figure 1.

HVA and MHPG plasma level assays

Plasma HVA levels were analyzed using high-performance liquid chromatography with electrochemical detection (HPLC-ECD) according to the method of Yeung et al[11] with slight modifications. In short, each cyano-bonded, solid-phase extraction cartridge was preconditioned with methanol followed by glass-distilled water. The plasma sample or standard solution and internal standard solution (5-hydroxyindolecarboxylic acid) were added to each cartridge. The samples were then deproteinized with acetonitrile. After vortexing and centrifugation, an aliquot of the supernatant was slowly drawn through the cartridge under a mild vacuum. The cartridge was washed twice with distilled water and extracted once with ethyl acetate. The aliquot was then evaporated with N_2. After being dissolved in the mobile phase (phosphate buffer), 10 µL of this solution was injected into the HPLC-ECD. The intra- and inter-assay coefficients of variation were 6% and 8%, respectively. The recovery rate was >80%.

The plasma MHPG levels were also analyzed by HPLC-ECD, according to the method of Minegishi and Ishizaki.[12] Briefly, after the plasma was separated by centrifugation, extraction was performed under a vacuum using Bond-Elut columns (Varian, Palo Alto, CA, USA) pre-packed with C18-bonded silica in a capacity disposable syringe. The columns, which were inserted into a vacuum chamber connected to an aspirator, were prepared by washing with 1 mL of methanol followed by 1 mL of water. After the addition of the internal standard (vanillyl alcohol) to the plasma, the samples were passed through the columns, followed by two rinses with distilled water to wash off any residual samples and easily eluted hydrophilic compounds. The adsorbed materials were eluted with methanol in a phosphate buffer mixture. A 20 µL portion of this solution was then injected into the HPLC-ECD. The intra- and inter-assay coefficients of variation were 6% and 8%, respectively. The recovery rate was >80%.

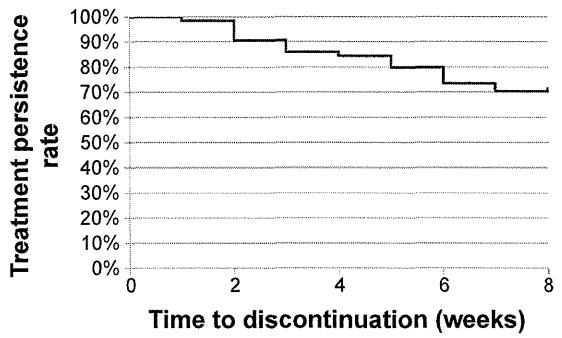

Figure 1 Treatment persistence rate.
Note: The persistence rate was calculated using the Kaplan–Meier method.

COMT Val158Met genotyping

Genomic DNA was extracted from peripheral leukocytes using a QIP DNA blood kit (Qiagen NV, Venlo, the Netherlands). The presence of the COMT Val158Met genotype was determined by sequencing of the genomic region.

Statistical analysis

The persistence rate was calculated using the Kaplan–Meier method. Non-paired *t*-tests were used to compare age, maximal daily duloxetine doses, number of major depressive episodes, HAMD17 scores, and plasma levels of catecholamine metabolites between the Val/Val group and the Met-carrier group among patients with MDD and healthy control subjects. Paired *t*-tests were performed to compare the plasma levels of catecholamine metabolites before (ie, at baseline) and after duloxetine treatment (8 weeks) between the Val/Val group and the Met-carrier group. *P*-values <0.05 were considered significant. All analyses were performed using SPSS version 19.0 (IBM Corporation, Armonk, NY, USA).

Results

The baseline plasma levels of HVA and MHPG in the patients with MDD were significantly lower than those in the healthy control subjects (Figure 2). Thirty of 45 patients (67%) responded to duloxetine treatment during the 8 weeks of treatment. However, there was no significant correlation between the changes in the total HAMD17 scores and the