Chapter 7
Electrophysiological Imaging Evaluation of Schizophrenia and Treatment Response

Tomiki Sumiyoshi, Yuko Higuchi, Toru Ito, and Yasuhiro Kawasaki

Abstract Neuroimaging data provide various insights into altered functions and structures in the brain of subjects with schizophrenia. While some blood flow measures, e.g. functional magnetic resonance imaging and positron emission tomography, are characterized by high spatial resolutions, their time resolutions are in the range of second order. In contrast, electromagnetic recordings, e.g. electroencephalography (EEG) and magnetoencephalography, directly detect neural activity that occurs in the range of milli-second order. In spite of its feasibility, analysis with traditional EEG methods has been associated with the limited ability to localize aberrant signals. However, the recent development of imaging technique, such as low resolution electromagnetic tomography (LORETA) and its modified versions (e.g. sLORETA), improves the spatial resolution of EEG at rest and event-related potentials (ERPs), such as P300 and mismatch negativity by providing three-dimensional distribution pattern of these electrophysiological activities. In this chapter, the authors present recent findings from electrical neuroimaging studies of schizophrenia in relation to the neural basis of psychotic symptoms and cognitive deficits of the illness, as well as treatment response. These research areas are likely to facilitate the development of practical and reliable biomarkers to predict symptom severity, improve long-term outcome, and pave a new avenue to early intervention of schizophrenia.

Keywords EEG · Event-related potentials · P300 · MMN · Neuro imaging · LORETA · Cognition · Schizophrenia

T. Sumiyoshi (✉)
Department of Neuropsychiatry, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, Toyama, Japan
e-mail: tomikisumiyoshi840@hotmail.com

M.S. Ritsner (ed.), *Handbook of Schizophrenia Spectrum Disorders, Volume III*,
DOI 10.1007/978-94-007-0834-1_7, © Springer Science+Business Media B.V. 2011

Abbreviations

AAPDs	Atypical antipsychotic drugs
EEG	Electroencephalography
LORETA	Low resolution electromagnetic tomography
MMN	Mismatch negativity

Introduction

There is considerable evidence for associations between social functioning/community outcome and cognitive function, as evaluated by neuropsychological tests, such as the MATRICS Consensus Cognitive Battery in patients with schizophrenia [1]. Therefore, neural substrates underlying impaired cognitive performance need to be elucidated, particularly for the development of novel therapeutic methods for the illness.

While brain imaging methods based on blood flow, e.g. functional magnetic resonance imaging and positron emission tomography, are characterized by high spatial resolutions, their time resolutions are limited compared to neurophysiological paradigms, e.g. electroencephalography (EEG) and magnetoencephalography. Specifically, electrophysiological biomarkers, such as EEG and event-related potentials (ERPs), have been suggested to provide objective indices of cognitive dysfunction in schizophrenia, and be more sensitive to drug-induced changes compared with other functional imaging modalities [2].

Recent development of imaging technique, such as low resolution electromagnetic tomography (LORETA) [3] and its modified versions (e.g. sLORETA) [4], has improved the spatial resolution of ERPs, e.g. P300 and mismatch negativity (MMN), by providing three-dimensional distribution pattern of these electrophysiological activities. This chapter provides recent findings from electrical neuroimaging studies on neural basis for psychopathology of schizophrenia as demonstrated by current source imaging of EEG and ERPs in discrete brain areas, and response to psychotropic drugs in relation to cognition and functional outcome.

LORETA Imaging of EEG in Schizophrenia

Scalp distributions of EEG power of various frequency bands are generally ambiguous [5], and depend on the reference sites used. Therefore, numerical analyses, such as dipole source modeling, are required to obtain precise locations of EEG generators.

LORETA has been developed to provide three-dimensional tomography of brain electrical activity, which only requires simple constraints ("smoothness of the solution"), and predetermined knowledge about the putative number of discernible source regions is not necessary (Fig. 7.1). With this method, brain electrical data

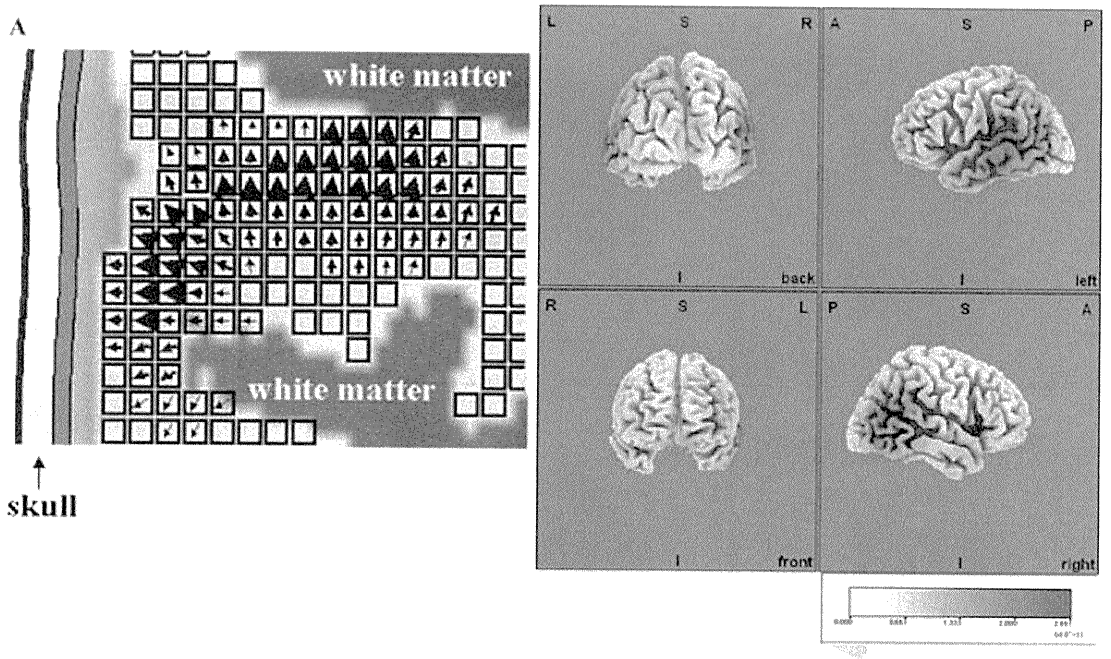

Fig. 7.1 Concept of low resolution electromagnetic tomography (LORETA) developed by Pascual-Marqui [3]. Three-dimensional imaging of LORETA values [mA/mm^2] is derived from 2394 voxels of the whole brain [8]

with high time resolution are transformed into functional imaging of brain activities, since brain electrical activity can be analyzed separately for the different EEG frequency ranges. LORETA has also been widely used for statistical comparisons of intracranial current density distributions between control subjects and patients with neuropsychiatric disorders [6, 7].

Previous investigations [3, 8] suggest that enhanced delta band activity in the prefrontal cortex is associated with the pathophysiology of schizophrenia. Specifically, negative symptoms have been associated with structural impairment in the prefrontal cortex, and have been hypothesized to arise from decreased dopaminergic activity in this brain region [9]. These observations indicate a role for prefrontal cortex in the generation of negative symptoms. With these backgrounds, we sought to determine if some components of EEG, such as delta band activity, would be increased in brain areas relevant to the pathophysiology of schizophrenia, e.g. prefrontal cortex.

As shown in Fig. 7.2 comparisons of current source density, as represented by LORETA values, between patients with schizophrenia and healthy control subjects revealed a significant increase in delta band activity for patients, with a maximum difference found at the left inferior temporal gyrus. A significant increase in delta band activities was also found for the right middle frontal gyrus, right inferior frontal gyrus, right superior frontal gyrus, and right parahippocampal gyrus. These data suggest LORETA analysis of three-dimensional distribution of EEG current density provides a measure of aberrant electrophysiological activity specific to the brain regions responsible for the manifestation of negative symptoms.

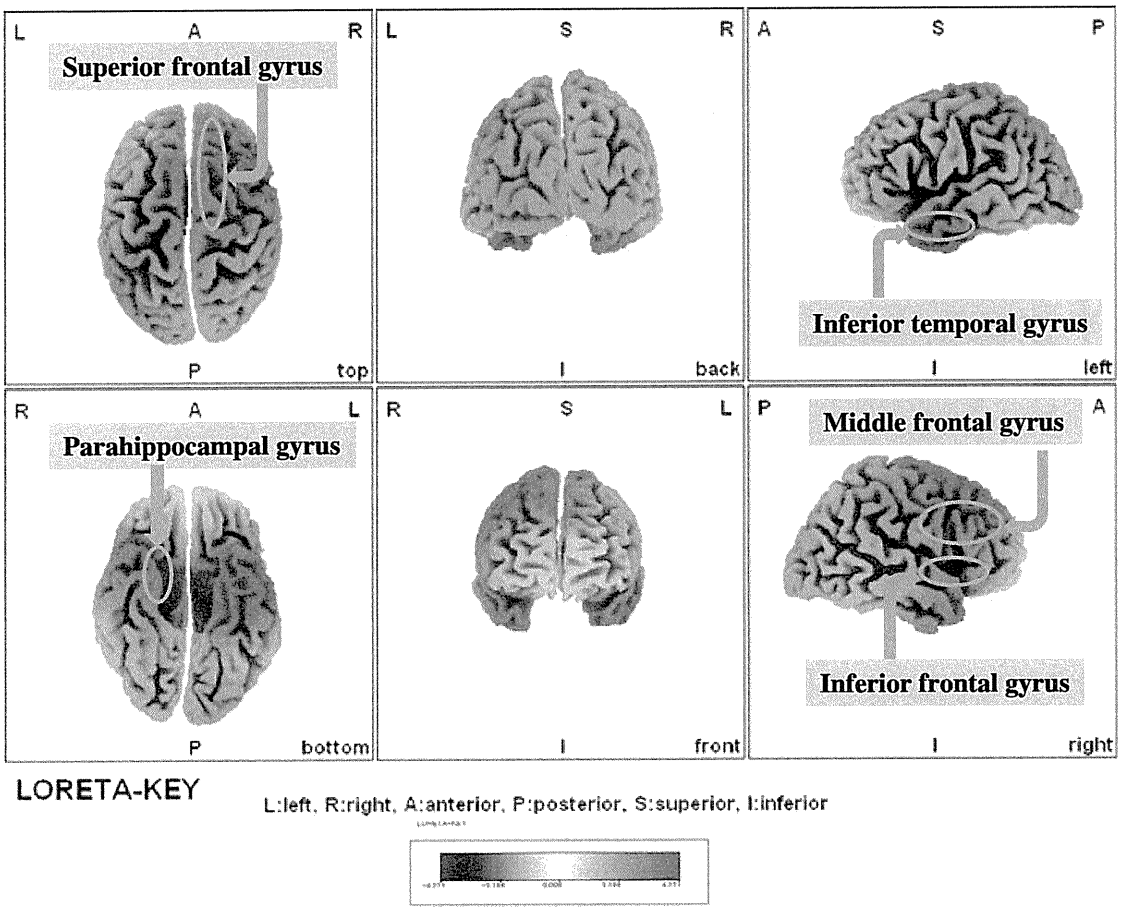

Fig. 7.2 LORETA current source density of *delta* band activity is increased in schizophrenia ($P < 0.001$, Bonferoni correction)

P300 Current Source Imaging and Psychopathology

Reduced amplitude of the P300 component during the auditory oddball task is one of the most consistent findings in patients with schizophrenia [10–12] (Fig. 7.3). However, little information is available about exact relationship between the clinical symptomatology of schizophrenia and the neurophysiological disturbances underlying the P300 abnormality. It is reasonable to assume that anatomically distinct neural substrates responsible for positive or negative symptoms independently contribute to the generation of the P300 component, because this ERP measure is thought to be a composite representation of neural activity in anatomically distinct generators [13–16].

To test this hypothesis, LORETA was used to compute the voxel-wise distribution of brain electrophysiological activity of the P300 component in order to identify brain regions in which the P300 current density is correlated with severity of psychotic symptoms of schizophrenia. Then, we applied the statistical parametric mapping (SPM) methods [17] to LORETA current density images of the P300 component [18, 19].

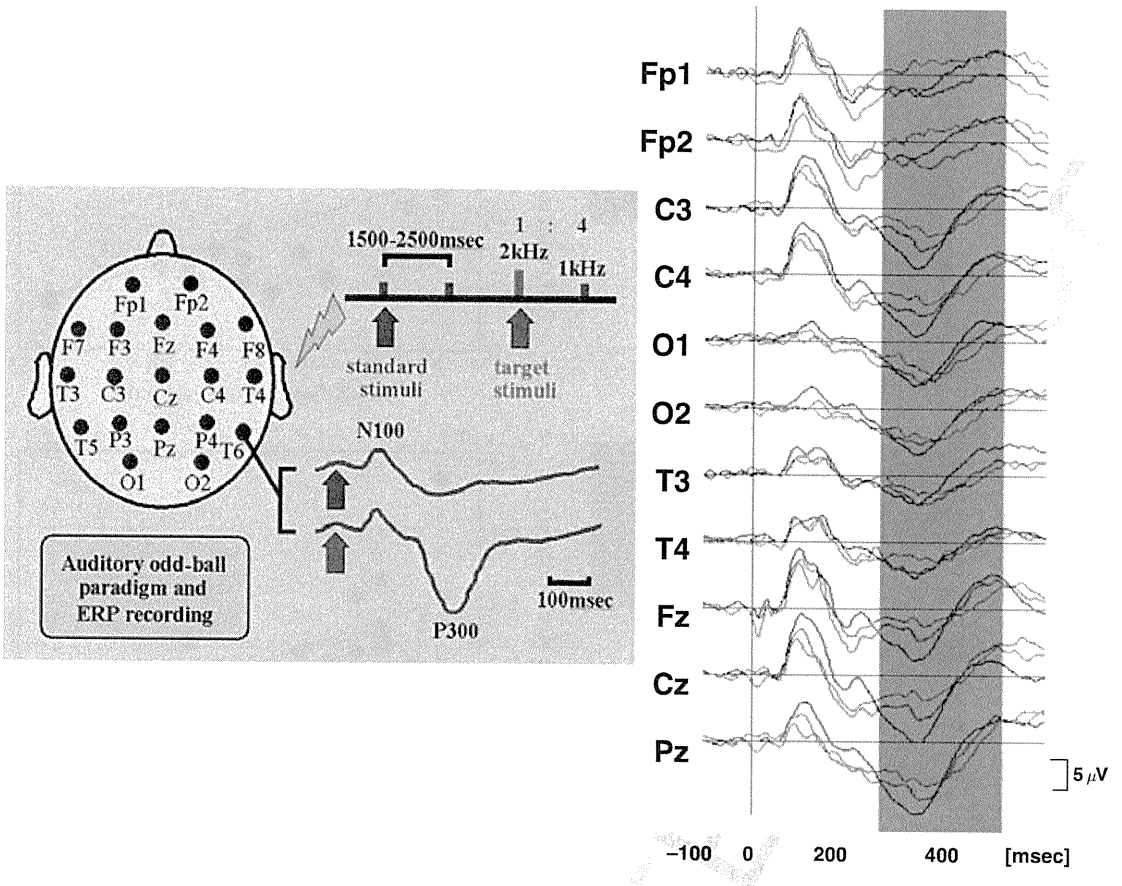

Fig. 7.3 Impaired P300, an event-related potential (ERP), as an endophenotypic marker of schizophrenia. In the right figure, black lines represent data for normal controls, while blue and red lines indicate data for patients before and after treatment with olanzapine, respectively

Results of the SPM one-sample t-test showed that P300 sources are localized in the bilateral medial frontal and medial parietal cortex, bilateral superior temporal gyrus (STG), right temporo-parietal junction, and left lateral prefrontal cortex. With regard to the relationship between the P300 current density and the BPRS Total score, voxel-based whole brain analysis without any hypothesis identified peak voxels of significant negative correlation located at the left STG and right medial frontal region. As shown in Fig. 7.4 (*left*), statistically significant voxels formed clusters within these brain regions. Mean current density values of the cluster in the STG elicited significant relationships with the Positive subscale score Fig. 7.4 (*right*). On the other hand, current density values of the cluster in the medial frontal region revealed a significant relationship with the Negative subscale score.

These findings indicate pathological neural activities of anatomically distinct generators contribute to the generation of the abnormal P300 component [20]. Our data were consistent with the proposal that negative symptoms are associated with neural deficits in the frontal lobe, while those in the temporal lobe are responsible for positive symptoms [21–23]. Taken together, the present results support the concept that the abnormal functional connectivity of fronto-temporal neural network plays a crucial role in the pathophysiology of schizophrenia [24–27].

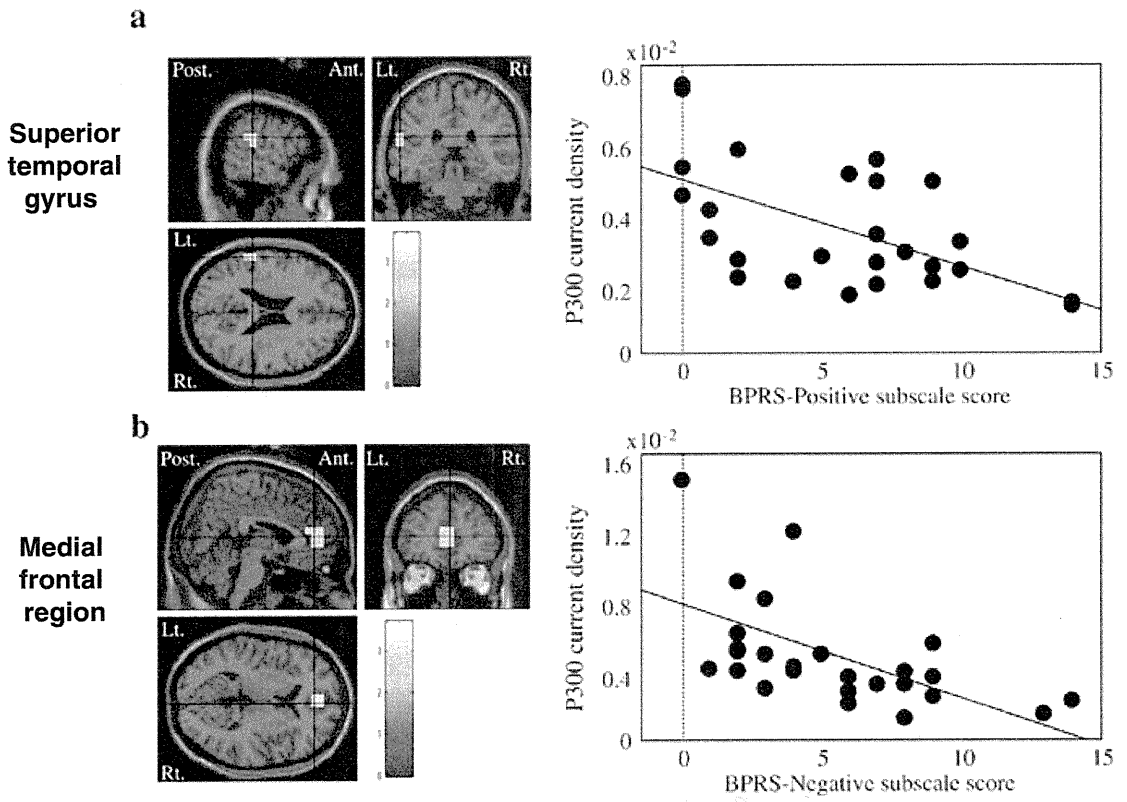

Fig. 7.4 Severity of psychotic symptoms is correlated with P300 current source density in discrete brain regions: A LORETA study [20]

ERPs Activity in Discrete Brain Regions and Effect of Neuroleptic Treatment

P300 amplitudes have been reported to be diminished in patients with schizophrenia, which differs in its effect size topography across the midline and temporal electrode sites [11, 28]. Specifically, Kawasaki et al. [29] found negative correlations between auditory P300 amplitudes and severity of psychotic symptoms of schizophrenia. Renoult et al. [30] report a positive correlation between differences in P300 amplitudes at temporal sites (T4-T3) and severity of positive symptoms and worse global functioning, consistent with the association between low P300 amplitudes and verbal memory deficits in schizophrenia [31, 32]. We reported the first observation that P300 current source density, as evaluated by LORETA, is decreased in several brain regions, especially the STG, precentral gyrus, middle frontal gyrus, and presumes (all in the left side) in patients with schizophrenia as compared with normal controls (Fig. 7.5) [33]. Our findings have been confirmed by an independent group of investigators [34].

Cognitive function, such as verbal memory, attention, and executive function, is a major determinant of outcome in patients with schizophrenia [35, 36]. The second generation antipsychotics, or so-called "atypical antipsychotic drugs (AAPDs)", have been found to partially improve cognitive disturbances of schizophrenia [37]. There is accumulated evidence for the ability of AAPDs, e.g. clozapine, olanzapine, risperidone, quetiapine, melperone, and ziprasidone and perospirone to ameliorate

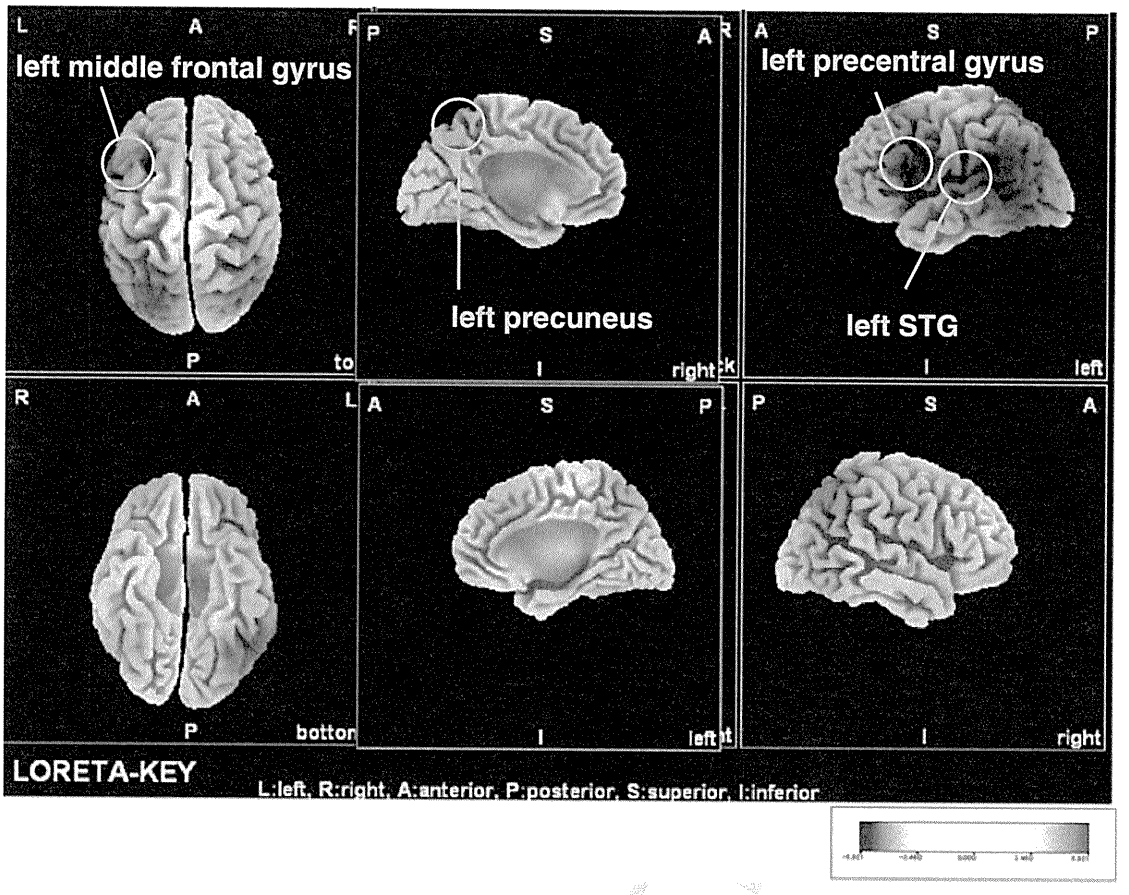

Fig. 7.5 Statistical non-parametric mapping on LORETA images of P300 current density. LORETA values in the marked areas in the left hemisphere were lower for schizophrenia patients compared to control subjects ($P < 0.001$) [33]

cognitive impairments in patients with schizophrenia (reviewed by Sumiyoshi et al. [38]), although their effects have been under scrutiny [39–41]. So far, there is limited information about the neurophysiological mechanisms underlying the ability of neuroleptic treatment to modulate cognitive performance in subjects with schizophrenia.

Umbricht et al. [42] found that treatment with clozapine but not haloperidol increased P300 amplitudes in patients with schizophrenia. Subsequently, Niznikiewicz et al. [43] observed an increase in P300 amplitudes in left temporal electrodes during treatment with clozapine, indicating a region-specific response to pharmacological treatment. We conducted clinical trials [33, 44] to determine if decreased P300 current source density in brain regions responsible for the generation of psychopathology, such as the left STG and prefrontal cortex, is recovered by long-term treatment with olanzapine, and if this change in P300 activity is correlated with improvement of cognitive performance and functional outcome in patients with schizophrenia.

As shown in Fig. 7.6 LORETA images of P300 from patients at baseline elicit lower P300 current density in the left hemisphere compared with normal controls. However, after 6-months treatment with olanzapine, P300 current density in the STG was increased, and the left-dominant laterality pattern of P300 current source

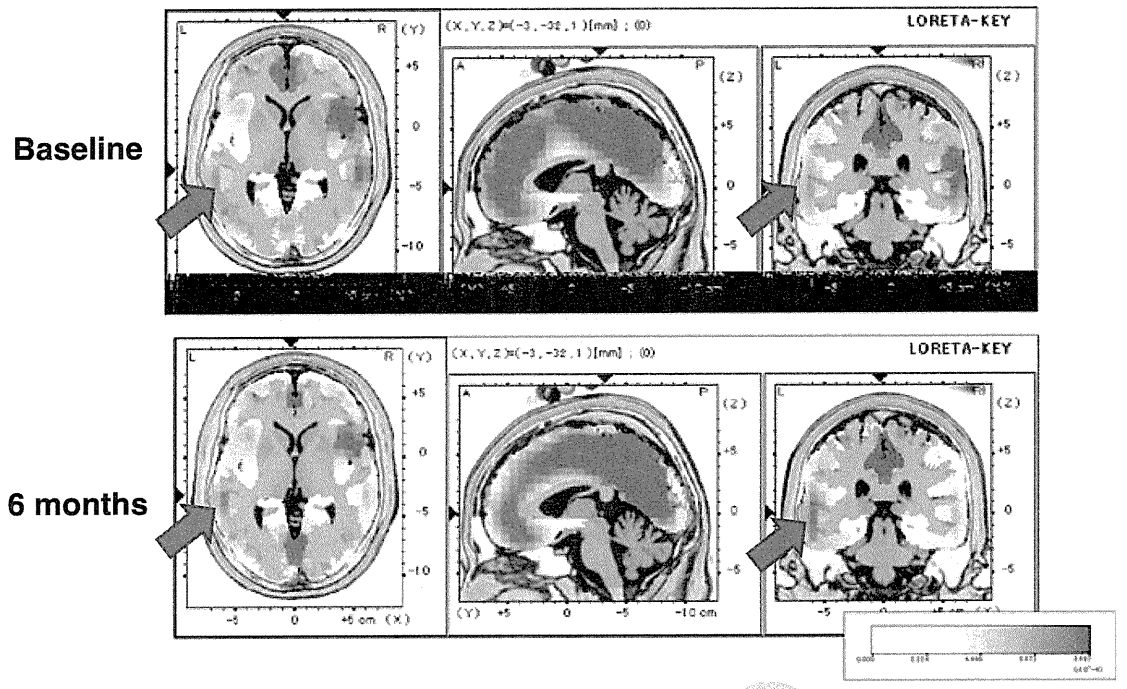

Fig. 7.6 LORETA images of P300; effect of olanzapine treatment. Six-month treatment with olanzapine enhanced P300 current source density in the left STG (indicated by *arrows*) [33]

density was noted, which is similar to the pattern of healthy controls [33, 44]. Moreover, significant correlations were noted between changes of verbal memory performance and LORETA values of the left STG, and between changes of quality of life and LORETA values of the left middle frontal gyrus (Fig. 7.7) [33]. These observations suggest that changes in cortical activity, as measured by EEG, are

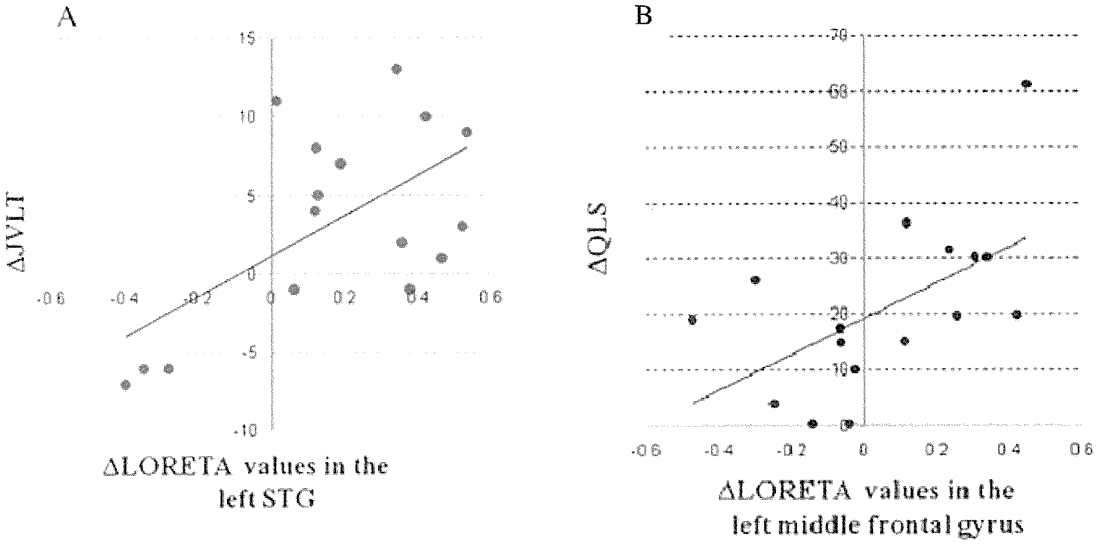

Fig. 7.7 (**A**) Changes in P300 current source density in the left STG by olanzapine were correlated with improvement in verbal memory, as measured by the Japanese Verbal learning Test (JVLT). (**B**) Changes in P300 current source density in the left middle frontal gyrus by olanzapine were correlated with improvement in quality of life, as measured by the Quality of Life Scale (QLS)

responsible for the ability of some antipsychotic drugs to improve cognitive and functional status in patients with schizophrenia.

From the clinical point of view, it is meaningful to examine the effect of type of antipsychotic drugs on the pattern of ERPs activation, as these compounds have been reported to possess differential profiles in terms of binding affinity for various neurotransmitter receptors [45]. Specifically, postmortem studies report that the serotonin-5-HT1A receptor density is increased in prefrontal cortical areas in subjects with schizophrenia [46, 47], suggesting altered 5-HT1A receptor-mediated transmission in this brain region [48, 49]. This concept is in agreement with clinical observations that augmentation therapy with 5-HT1A partial agonists, e.g. buspirone and tandospirone, enhanced the performance on some neuropsychological tests representing frontal lobe function in patients with schizophrenia [38, 50]. Therefore, it is conceivable that neural activity in frontal cortical regions would be enhanced by treatment with antipsychotic drugs with agonist actions at 5-HT1A receptors, such as perospirone [45], in patients with schizophrenia.

Using the same treatment paradigm as in the olanzapine study, above, we investigated the effect of perospirone on P300 current source density, as evaluated by the sLORETA method [4], in patients with schizophrenia, and examine the relationship between changes of P300 activity vs. performance on a cognitive task measuring the ability to evaluate component actions of social situations, which is related to frontal lobe function. As shown in Fig. 7.8 comparison of P300 current source density between baseline and 6-month after the start of treatment revealed a significantly enhanced neural activity in the left superior frontal gyrus, while conventional assessment of P300 amplitudes and latency were not significantly changed [51]. Some of the subjects studied here had been pre-treated with other antipsychotic drugs, including olanzapine, which are devoid of a noticeable affinity for 5-HT1A receptors. Therefore, our observations with perospirone provide further support to the

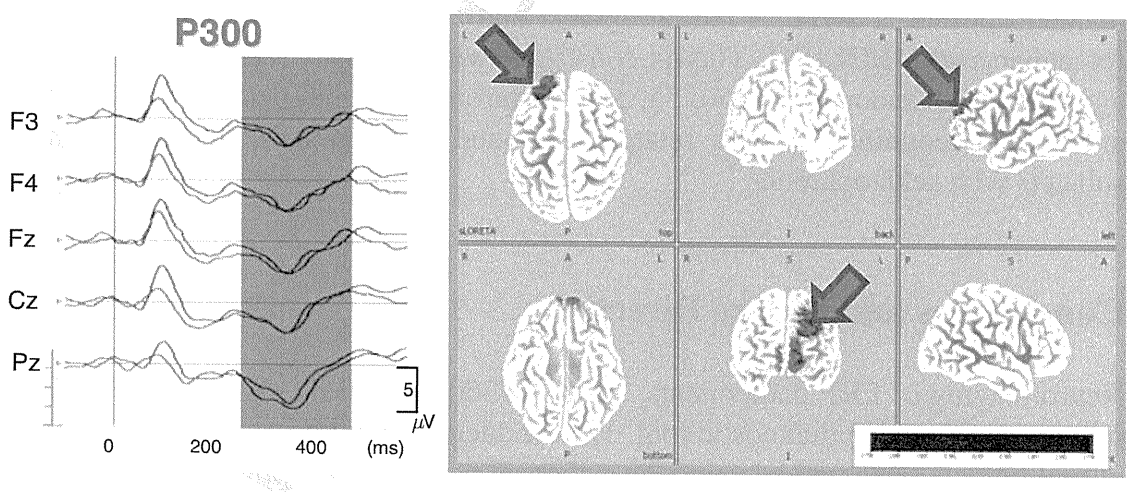

Fig. 7.8 Effect of perospirone on P300 current source density in patients with schizophrenia. Six-month treatment with perospirone enhanced P300 activity in the left superior frontal gyrus (comparison of P300 sLORETA values between before and after 6-month treatment) [51]

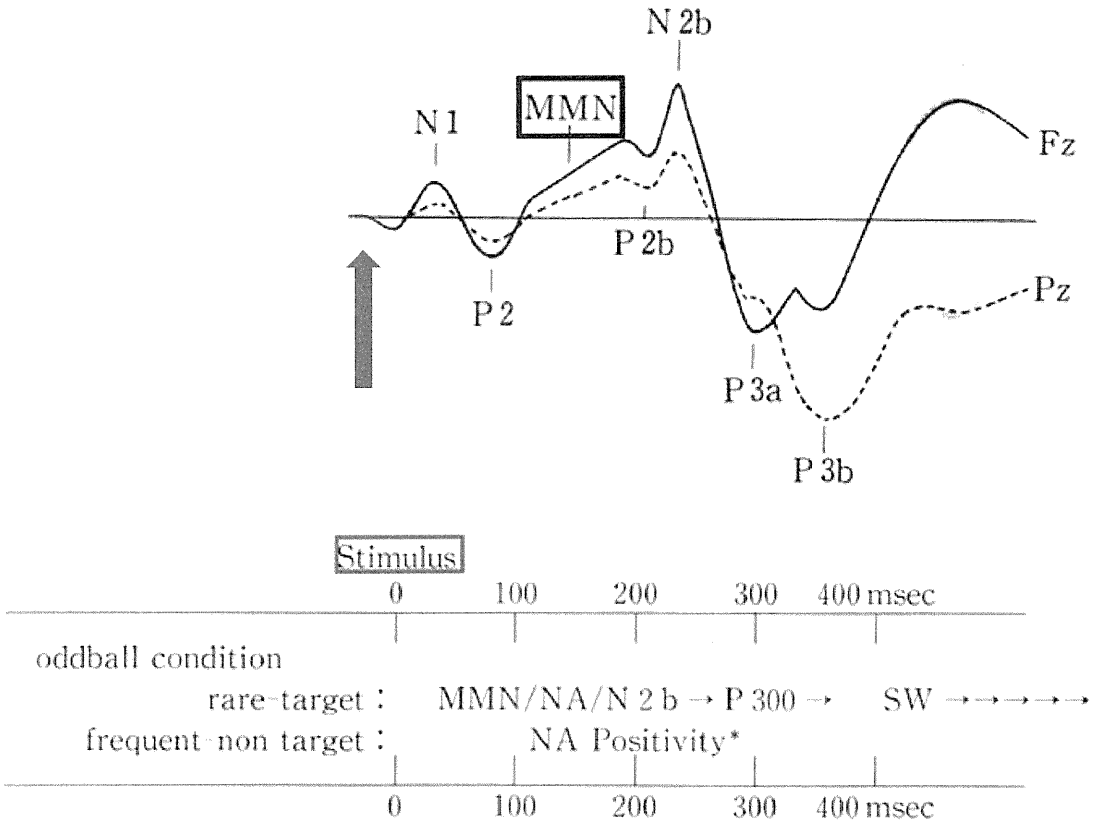

Fig. 7.9 ERP waveforms in response to the odd-ball tasks (rare-target)

concept that stimulation of 5-HT1A receptors may mediate the ability of this agent to increase P300 current source density in the left prefrontal cortex.

Mismatch negativity (MMN) is another component of ERPs generated in response to occasional variations of acoustic stimuli (Fig. 7.9) and is suggested to reflect *pre-attentive* cognitive operations [52]. We recently found the addition of tandospirone, a 5-HT1A partial agonist and anxiolytic [50, 53], was effective for enhancing MMN [54]. This is consistent with previous reports that 5-HT1A agonists, e.g., tandospirone [50, 53, 55], buspirone [38], and perospirone [51, 56], ameliorated cognitive deficits related to frontal and temporal lobe function in subjects with schizophrenia.

Conclusions and Future Directions

Neuroimaging of ERP components, such as P300 and MMN, are also expected to provide an objective diagnostic tool. We conducted discriminant function analysis of multivariate linear model using the statistical parametric mapping (SPM) in order to construct an optimal model to distinguish between healthy controls and patients with chronic schizophrenia [57] (Fig. 7.10). Although the classification power was not enough due, possibly, to the fact that these patients were mixed in terms of

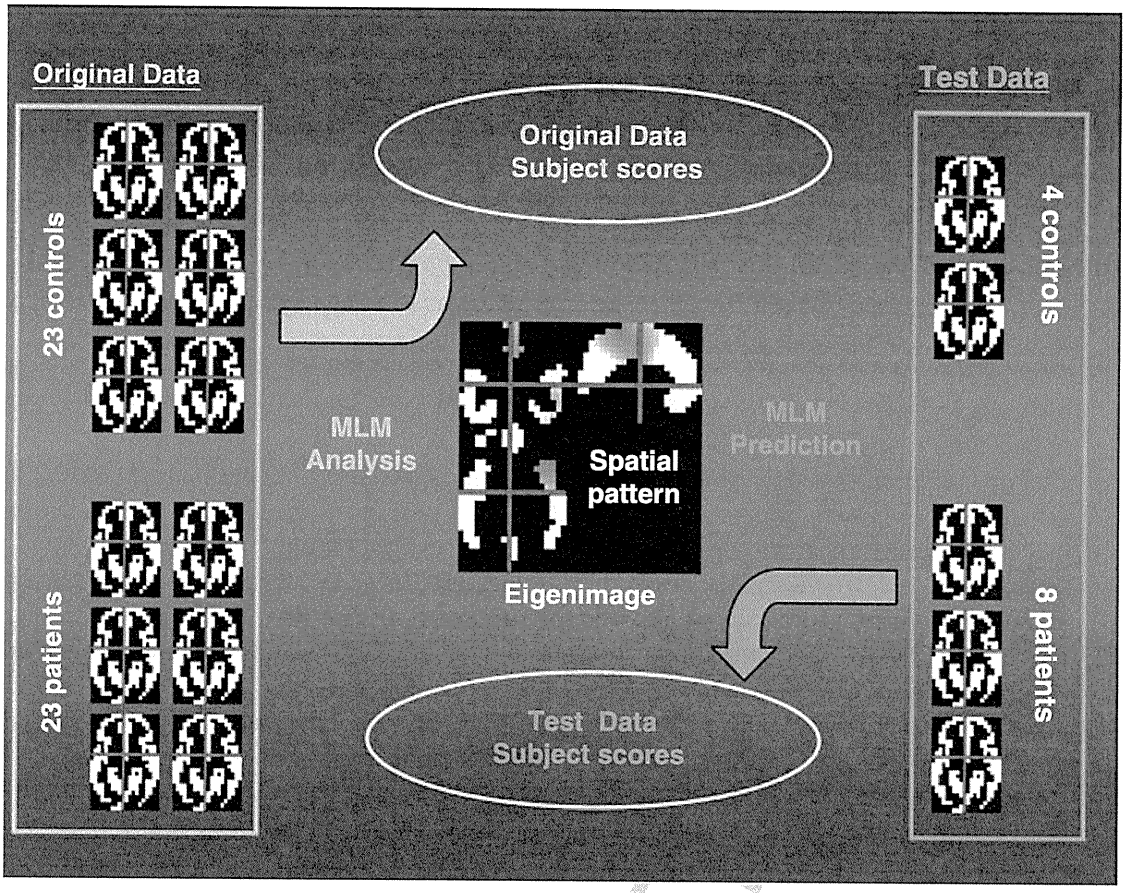

Fig. 7.10 The general scheme of discriminant function analysis of multivariate linear model (MLM) *using the* statistical parametric mapping [57]

treatment status [57], application of this method to drug-naïve subjects with first episode schizophrenia and those at the prodromal stage is likely to facilitate early intervention into the illness.

In conclusion, the utilization of neuroimaging methods enhances spatial resolution of electrophysiological evaluation, e.g. ERPs, which would provide feasible and reliable biomarkers, objective assessments of psychosis and cognition, and predictive measures of treatment response, and facilitate early diagnosis and intervention of schizophrenia.

Acknowledgments This work was supported by grants-in-aid for Scientific Research from Japan Society for the Promotion of Science and grants-in-aid from the Ministry of Health, Labour and Welfare, Japan.

References

1. Green MF, Kern RS, Heaton RK (2004) Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. Schizophr Res 72:41–51
2. Javitt DC, Spencer KM, Thaker GK et al (2008) Neurophysiological biomarkers for drug development in schizophrenia. Nat Rev Drug Discov 7:68–83

3. Pascual-Marqui RD, Lehmann D, Koenig T et al (1999) Low resolution brain electromagnetic tomography (LORETA) functional imaging in acute, neuroleptic-naive, first-episode, productive schizophrenia. Psychiatry Res 90:169–179
4. Pascual-Marqui RD (2002) Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. Methods Find Exp Clin Pharmacol 24(Suppl D):5–12
5. Pascual-Marqui RD (1999) Review of methods for solving the EEG inverse problem. Int J Bioelectromagnetism 1:75–86
6. Pizzagalli D, Pascual-Marqui RD, Nitschke JB et al (2001) Anterior cingulate activity as a predictor of degree of treatment response in major depression: evidence from brain electrical tomography analysis. Am J Psychiatry 158:405–415
7. Flor-Henry P, Lind JC, Koles ZJ (2004) A source-imaging (low-resolution electromagnetic tomography) study of the EEGs from unmedicated males with depression. Psychiatry Res 130:191–207
8. Mientus S, Gallinat J, Wuebben Y et al (2002) Cortical hypoactivation during resting EEG in schizophrenics but not in depressives and schizotypal subjects as revealed by low resolution electromagnetic tomography (LORETA). Psychiatry Res 116:95–111
9. Lynch MR (1992) Schizophrenia and the D1 receptor: focus on negative symptoms. Prog Neuropsychopharmacol Biol Psychiatry 16:797–832
10. Braff DL (1993) Information processing and attention dysfunctions in schizophrenia. Schizophr Bull 19:233–259
11. Jeon YW, Polich J (2003) Meta-analysis of P300 and schizophrenia: patients, paradigms, and practical implications. Psychophysiology 40:684–701
12. Roth WT, Cannon EH (1972) Some features of the auditory evoked response in schizophrenics. Arch Gen Psychiatry 27:466–471
13. Anderer P, Saletu B, Semlitsch HV et al (2003) Non-invasive localization of P300 sources in normal aging and age-associated memory impairment. Neurobiol Aging 24:463–479
14. Mulert C, Pogarell O, Juckel G et al (2004) The neural basis of the P300 potential. Focus on the time-course of the underlying cortical generators. Eur Arch Psychiatry Clin Neurosci 254:190–198
15. Wang J, Hiramatsu K, Hokama H et al (2003) Abnormalities of auditory P300 cortical current density in patients with schizophrenia using high density recording. Int J Psychophysiol 47:243–253
16. Winterer G, Mulert C, Mientus S et al (2001) P300 and LORETA: comparison of normal subjects and schizophrenic patients. Brain Topogr 13:299–313
17. Friston KJ (1995) Commentary and opinion:II. Statistical parametric mapping: ontology and current issues. J Cereb Blood Flow Metab 15:361–370
18. Pae JS, Kwon JS, Youn T et al (2003) LORETA imaging of P300 in schizophrenia with individual MRI and 128-channel EEG. NeuroImage 20:1552–1560
19. Park HJ, Kwon JS, Youn T et al (2002) Statistical parametric mapping of LORETA using high density EEG and individual MRI: application to mismatch negativities in schizophrenia. Hum Brain Mapp 17:168–178
20. Kawasaki Y, Sumiyoshi T, Higuchi Y et al (2007) Voxel-based analysis of P300 electrophysiological topography associated with positive and negative symptoms of schizophrenia. Schizophr Res 94:164–171
21. Andreasen NC (1982) Negative symptoms in schizophrenia: definition and reliability. Arch Gen Psychiatry 39:789–794
22. Crow TJ (1980) Positive and negative schizophrenic symptoms and dopamine. Br J Psychiatry 137:383–386
23. Liddle PF (1987) The symptoms of chronic schizophrenia. A re-examination of the positive-negative dichotomy. Br J Psychiatry 151:145–151
24. Friston KJ, Frith CD (1995) Schizophrenia: a disconnection syndrome? Clin Neurosci 3: 89–97

25. Kurachi M (2003) Pathogenesis of schizophrenia: part II. Temporo-frontal two-step hypothesis. Psychiatry Clin Neurosci 57:9–15
26. Lawrie SM, Buechel C, Whalley HC et al (2002) Reduced frontotemporal functional connectivity in schizophrenia associated with auditory hallucinations. Biol Psychiatry 51:1008–1011
27. Meyer-Lindenberg A, Miletich RS, Kohn PD et al (2002) Reduced prefrontal activity predicts exaggerated striatal dopaminergic function in schizophrenia. Nat Neurosci 28:28
28. Bruder G, Kayser J, Tenke C et al (1999) Left temporal lobe dysfunction in schizophrenia: event-related potential and behavioral evidence from phonetic and tonal dichotic listening tasks. Arch Gen Psychiatry 56:267–276
29. Kawasaki Y, Maeda Y, Higashima M et al (1997) Reduced auditory P300 amplitude, medial temporal volume reduction and psychopathology in schizophrenia. Schizophr Res 26:107–115
30. Renoult L, Prevost M, Brodeur M et al (2007) P300 asymmetry and positive symptom severity: a study in the early stage of a first episode of psychosis. Schizophr Res 93:366–373
31. Nagasawa T, Kamiya T, Kawasaki Y et al (1999) The relationship between auditory ERP and neuropsychological assessments in schizophrenia. Int J Psychophysiol 34:267–274
32. Nieman DH, Koelman JH, Linszen DH et al (2002) Clinical and neuropsychological correlates of the P300 in schizophrenia. Schizophr Res 55:105–113
33. Higuchi Y, Sumiyoshi T, Kawasaki Y et al (2008) Electrophysiological basis for the ability of olanzapine to improve verbal memory and functional outcome in patients with schizophrenia: a LORETA analysis of P300. Schizophr Res 101:320–330
34. Wang J, Tang Y, Li C et al (2010) Decreased P300 current source density in drug-naive first episode schizophrenics revealed by high density recording. Int J Psychophysiol 75: 249–257
35. Meltzer HY, Sumiyoshi T (2003) Atypical antipsychotic drugs improve cognition in schizophrenia. Biol Psychiatry 53:265–267; author reply, 267–268
36. Sumiyoshi T, Meltzer H (2003) Pharmacological strategy for enhancement of social function and quality of life in patients with schizophrenia: considerations of the effect of melperone, an atypical antipsychotic drug, on cognitive function. Seishin-igaku 45:1279–1284
37. Keefe RS, Sweeney JA, Gu H et al (2007) Effects of olanzapine, quetiapine, and risperidone on neurocognitive function in early psychosis: a randomized, double-blind 52-week comparison. Am J Psychiatry 164:1061–1071
38. Sumiyoshi T, Park S, Jayathilake K et al (2007) Effect of buspirone, a serotonin1A partial agonist, on cognitive function in schizophrenia: a randomized, double-blind, placebo-controlled study. Schizophr Res 95:158–168
39. Woodward ND (2006) A meta-analysis of neuropsychological change with second generation antipsychotics in schizophrenia. 24th CINP congress. Chicago, USA
40. Woodward ND, Purdon SE, Meltzer HY et al (2005) A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. Int J Neuropsychopharmacol 8:457–472
41. Keefe RS, Bilder RM, Davis SM et al (2007) Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE trial. Arch Gen Psychiatry 64:633–647
42. Umbricht D, Javitt D, Novak G et al (1998) Effects of clozapine on auditory event-related potentials in schizophrenia. Biol Psychiatry 44:716–725
43. Niznikiewicz MA, Patel JK, McCarley R et al (2005) Clozapine action on auditory P3 response in schizophrenia. Schizophr Res 76:119–121
44. Sumiyoshi T, Higuchi Y, Kawasaki Y et al (2006) Electrical brain activity and response to olanzapine in schizophrenia: a study with LORETA images of P300. Prog Neuropsychopharmacol Biol Psychiatry 30:1299–1303
45. Sumiyoshi T (2008) A possible dose-side effect relationship of antipsychotic drugs: relevance to cognitive function in schizophrenia. Expert Rev Clin Pharmacol 1:791–802
46. Hashimoto T, Nishino N, Nakai H et al (1991) Increase in serotonin 5HT1A receptors in prefrontal and temporal cortices of brains from patients with chronic schizophrenia. Life Sci 48:355–363

47. Sumiyoshi T, Stockmeier CA, Overholser JC et al (1996) Serotonin1A receptors are increased in postmortem prefrontal cortex in schizophrenia. Brain Res 708:209–214
48. Sumiyoshi T, Meltzer HY (2004) Serotonin 1A receptors in memory function. Am J Psychiatry 161:1505
49. Sumiyoshi T, Bubenikova-Valesova V, Horacek J et al (2008) Serotonin1A receptors in the pathophysiology of schizophrenia: development of novel cognition-enhancing therapeutics. Adv Ther 25:1037–1056
50. Sumiyoshi T, Matsui M, Nohara S et al (2001) Enhancement of cognitive performance in schizophrenia by addition of tandospirone to neuroleptic treatment. Am J Psychiatry 158:1722–1725
51. Sumiyoshi T, Higuchi Y, Itoh T et al (2009) Effect of perospirone on P300 electrophysiological activity and social cognition in schizophrenia: a three-dimensional analysis with sloreta. Psychiatry Res 172:180–183
52. Garrido MI, Kilner JM, Stephan KE et al (2009) The mismatch negativity: a review of underlying mechanisms. Clin Neurophysiol 120:453–463
53. Sumiyoshi T, Matsui M, Yamashita I et al (2000) Effect of adjunctive treatment with serotonin-1A agonist tandospirone on memory functions in schizophrenia [letter]. J Clin Psychopharmacol 20:386–388
54. Higuchi Y, Sumiyoshi T, Kawasaki T et al (2010) Effect of tandospirone on mismatch negativity and cognitive performance in schizophrenia: a case report. J Clin Psychopharmacol 30: 732–734
55. Sumiyoshi T, Matsui M, Yamashita I et al (2001) The effect of tandospirone, a serotonin(1A) agonist, on memory function in schizophrenia. Biol Psychiatry 49:861–868
56. Araki T, Yamasue H, Sumiyoshi T et al (2006) Perospirone in the treatment of schizophrenia: effect on verbal memory organization. Prog Neuropsychopharmacol Biol Psychiatry 30: 204–208
57. Kawasaki Y, Sumiyoshi T, Higuchi Y et al (2006) Can event-related potentials be of diagnostici value for schizophrenia? Association of European psychiatrists-14th European congress of psychiatry, Nice

HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol Clin Exp 2012; **27**: 90–100.
Published online in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/hup.1276

Effect of blonanserin on cognitive function in antipsychotic-naïve first-episode schizophrenia

Tomomi Tenjin[1]*, Seiya Miyamoto[1], Nobumi Miyake[1], Shin Ogino[1], Rei Kitajima[1], Kazuaki Ojima[1], Jun Arai[1], Haruki Teramoto[1], Sachiko Tsukahara[1], Yukie Ito[1], Masanori Tadokoro[1], Kiriko Anai[1], Yasuyuki Funamoto[2], Yasuhiro Kaneda[3], Tomiki Sumiyoshi[4] and Noboru Yamaguchi[1]

[1]*Department of Neuropsychiatry, St. Marianna University School of Medicine, Kawasaki, Kanagawa Japan*
[2]*Department of Psychiatry, Ofuji Hospital, Fuji, Shizuoka Japan*
[3]*Department of Psychiatry, Iwaki Clinic, Anan, Tokushima Japan*
[4]*Department of Neuropsychiatry, University of Toyama, Toyama, Japan*

Objective The purpose of this study was to evaluate the effects of blonanserin, a novel antipsychotic, on cognitive function in first-episode schizophrenia.
Methods Twenty-four antipsychotic-naïve patients with first-episode schizophrenia participated in the study. Blonanserin was given in an open-label design for 8 weeks. The Brief Assessment of Cognition in Schizophrenia—Japanese language version (BACS-J) was administered as the primary outcome measure at baseline and 8 weeks. Clinical evaluation included the Positive and Negative Syndrome Scale (PANSS), the Schizophrenia Quality of Life Scale—Japanese language version (SQLS-J), and the Clinical Global Impression—Severity of Illness Scale (CGI-S). To exclude the possibility of retest effects on the BACS-J, 10 age-matched patients with chronic schizophrenia treated with blonanserin were tested at baseline and after an 8-week interval.
Results Twenty first-episode patients completed the study. Repeated measures analysis of covariance revealed a significant group-by-time interaction effect on the letter fluency task due to better performance in the first-episode group, but not in the control group. Main effect of time or group-by-time interaction effect on the Tower of London task was not significant; however, the first-episode group, but not the control group, showed substantial improvement with a moderate effect size. All items on the PANSS, SQLS-J, and CGI-S significantly improved after 8 weeks of treatment.
Conclusions These results suggest that blonanserin improves some types of cognitive function associated with prefrontal cortical function.
Copyright © 2012 John Wiley & Sons, Ltd.

KEY WORDS—blonanserin; cognition; quality of life; schizophrenia; letter fluency

INTRODUCTION

Cognitive impairment is a core feature of schizophrenia (Gold and Harvey, 1993; Green *et al.*, 2000) and is present early in the course of the illness (Mesholam-Gately *et al.*, 2009; Bozikas and Andreou, 2011). A number of studies have reported a 1–2 standard deviation (SD) decline in the performance on tests of multiple cognitive domains, including attention, executive function, memory, and processing speed, compared with healthy volunteers (Saykin *et al.*, 1994; Bilder *et al.*, 2000; Wolwer *et al.*, 2008; Mesholam-Gately *et al.*, 2009). These cognitive deficits have been shown to largely determine social and occupational functioning (Green, 1996; Meltzer *et al.*, 1996), as well as quality of life (QOL) in patients with schizophrenia (Matsui *et al.*, 2008; Tomida *et al.*, 2010; Woon *et al.*, 2010). Given that cognitive deficits are among the strongest predictors of functional outcome in schizophrenia (Green *et al.*, 2000), treatments for these symptoms are most urgently needed (Sumiyoshi *et al.*, 2008; Miyamoto *et al.*, in press).

A renewed interest in the amelioration of cognitive impairment associated with schizophrenia arose with the introduction of new antipsychotic drugs. Earlier reviews suggested that the second-generation antipsychotics (SGAs) may have more beneficial effects on cognition than the first-generation antipsychotics (FGAs) (Keefe *et al.*, 1999; Harvey and Keefe, 2001; Mishara and Goldberg, 2004). However, several confounding factors, such as incomparable antipsychotic doses, heterogeneous patient samples, effects of prior medication, lack of control for retest effects on cognitive measures, and adjunctive anticholinergic medication,

*Correspondence to: T. Tenjin, MD, Department of Neuropsychiatry, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki, Kanagawa 216-8511, Japan. Tel: +81 44 977 8111; Fax: +81 44 976 3341. E-mail: t2tenjin@marianna-u.ac.jp

Received 14 September 2011
Revised 23 November 2011
Accepted 21 December 2011

Copyright © 2012 John Wiley & Sons, Ltd.

limit the conclusions that can be drawn regarding the effects of different antipsychotic drugs on cognition (Carpenter and Gold, 2002; Goldberg *et al.*, 2007, 2010; Hill *et al.*, 2010; Andersen *et al.*, 2011). Recent large controlled studies have demonstrated significant cognitive improvement with both FGAs and SGAs from baseline, but neither class appeared to be clearly superior to the other, and the magnitude of cognitive improvement was modest at best (Keefe *et al.*, 2007a, 2007b; Davidson *et al.*, 2009).

Blonanserin, 2-(4-ethyl-1-piperazinyl)-4-(4-fluorophenyl)-5,6,7,8,9,10-hexahy-drocycloocta [b] pyridine, was developed as a novel antipsychotic drug in Japan (Noda *et al.*, 1993; Oka *et al.*, 1993) and was approved for the treatment of schizophrenia in Japan and Korea (Deeks and Keating, 2010). It has high affinity for dopamine $D_{2,3}$ and serotonin 5-HT_{2A} receptors but shows low affinity for $D_{1,4,5}$, adrenergic $\alpha_{1,2}$, β, 5-$HT_{1A,2B,2C,3-7}$ histamine H_1, and muscarinic M_1 receptors (Oka *et al.*, 1993; Deeks and Keating, 2010). A preclinical study demonstrated that blonanserin increased extracellular levels of dopamine and norepinephrine in the prefrontal cortex (Ohoyama *et al.*, 2011). In three randomized, 8-week, double-blind clinical trials, blonanserin was equal to haloperidol and risperidone in primary endpoints (final global improvement rate or improvement in total symptomatology) and was superior to haloperidol in improving negative symptoms in patients with schizophrenia (Murasaki, 2007a; Miura, 2008; Yang *et al.*, 2010). The overall tolerability profile of blonanserin was similar to that of haloperidol and risperidone (Murasaki, 2007a; Miura, 2008; Deeks and Keating, 2010; Yang *et al.*, 2010), but blonanserin was associated with a lower incidence of extrapyramidal symptoms (EPS) than haloperidol (Murasaki, 2007a). In our previous randomized, double-blind, 8-week study comparing blonanserin with risperidone, blonanserin significantly improved certain cognitive functions such as verbal memory, attention, and processing speed in patients with chronic schizophrenia (Miyake *et al.*, 2008).

To date, no study has examined the effects of blonanserin on clinical efficacy including cognitive function in first-episode schizophrenia. Given the above-mentioned observations from basic and clinical studies, it is hypothesized that treatment with blonanserin would improve some domains of cognitive function, probably those associated with prefrontal cortical function, in patients with first-episode schizophrenia. To test this hypothesis, this study was conducted to evaluate the effects of blonanserin on clinical symptoms and subjective QOL in patients with antipsychotic-naïve first-episode schizophrenia.

METHODS

This prospective, single-blind, open-label study was conducted at St. Marianna University School of Medicine Hospital and Ofuji Hospital from March 2009 to July 2011. It was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the St. Marianna University School of Medicine Bioethics Committee. All participants gave informed consent after the study procedures had been fully explained.

Study participants

Twenty-four subjects (13 male and 11 female) participated in this study. Eligible participants were inpatients and outpatients with a clinical diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000), who met the following inclusion criteria: (i) aged 16 to 40 years; (ii) experiencing their first episode of psychosis for at least 1 month and less than 5 years; and (iii) no history of antipsychotic exposure or, if previously treated, a total lifetime of antipsychotic treatment of less than 16 weeks and no antipsychotic administration for 12 weeks before participating in the study. Most of the inclusion criteria were based on previous first-episode studies (Keefe *et al.*, 2007b; McEvoy *et al.*, 2007; Perkins *et al.*, 2008). Diagnosis was performed using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders.

Exclusion criteria were as follows: (i) patients who had been treated with blonanserin before study entry; (ii) comorbid central nervous system disorder; (iii) meeting the DSM-IV-TR criteria for current and/or past alcohol or other substance dependence or abuse; (iv) meeting the DSM-IV-TR criteria for mental retardation; (v) taking tricyclic antidepressants; (vi) treatment with electroconvulsive therapy in the 12 weeks preceding the study; (vii) patients who were not voluntarily hospitalized; (viii) active expression of suicidal or homicidal ideation; (ix) pregnancy or breast feeding; and (x) inability to understand the study protocol or if the subject was judged to be uncooperative by the rater.

To exclude possible retest effects on cognitive measures, 10 patients with chronic schizophrenia (five male and five female) who matched for age, sex, and education were recruited as a control group (Table 1). Inclusion criteria for the control group were as follows: (i) patients who have been treated with a stable dose of blonanserin as monotherapy for at least 12 weeks; (ii)

Copyright © 2012 John Wiley & Sons, Ltd.

Table 1. Baseline demographic and clinical characteristics among first-episode schizophrenia and control group subjects

	First-episode group ($n=20$)	Control group ($n=20$)	Significance[c]
Gender (male/female)	10/10	5/5	NS[d]
Age[a] (years)	26.1 (6.2)	26.9 (6.6)	NS
Education level[a] (years)	13.8 (2.0)	13.2 (1.4)	NS
Duration of untreated psychosis[a] (months)	8.1 (11.8)	15.2 (13.8)	NS
Benzodiazepine dose[a] (mg/day)	0.7 (1.7)	0.8 (1.6)	NS
PANSS			
Positive score	23.8 (4.0)	15.4 (3.7)	NS
Negative score	29.5 (6.4)	18.2 (5.7)	NS
General psychopathology score	56.9 (8.1)	37.3 (10.5)	NS
Total score	109.7 (16.0)	70.9 (18.0)	NS

NS, no significant difference; PANSS, Positive and Negative Syndrome Scale.
[a]Values represent mean (SD).
[b]Lorazepam-equivalent dose.
[c]Independent *t*-test.
[d]Chi-squared test.

aged 16 to 40 years; (iii) having a history of psychotic relapses; and (iv) duration of illness of at least 2 years. Exclusion criteria for the control group were the same as those of the first-episode patients, except for blonanserin treatment.

Study design

Twenty-four subjects were initially recruited to the present study and assigned to the first-episode schizophrenia group (first-episode group). Subsequently, 10 subjects were recruited and assigned to the control group (control group).

In the first-episode group, blonanserin was orally administered for 8 weeks. The manufacturer recommends twice daily administration of blonanserin (Deeks and Keating, 2010). However, the half-life of blonanserin was reported to be 67.9 h after repeated administrations at 4 mg/day for 10 days in healthy individuals (Deeks and Keating, 2010). Thus, in this study, blonanserin was administered once or twice daily after meal intake. While the approved dose range of blonanserin is 8–24 mg/day, first-episode patients generally respond more to lower antipsychotic doses than do patients with recurrent episodes (Miyamoto *et al.*, 2008; Salimi *et al.*, 2009). Thus, patients initially received a low dose of blonanserin (2–6 mg/day), but the dosage was adjusted to between 2 and 24 mg/day according to the treating physician's discretion. In the control group, the dose of blonanserin was fixed during the trial.

Benzodiazepines, sedative-hypnotics, antidepressants except for tricyclic antidepressants, and/or mood stabilizers were allowed if clinically needed, but they were kept to a minimum during the study (Table 2). Whenever clinically significant EPS occurred, anticholinergic drugs were allowed. However, clinicians were encouraged to lower the dose of blonanserin to relieve EPS. There was no limit to the biperiden-equivalent dose that could be prescribed. Prophylactic administration of anticholinergic drugs and additional antipsychotics were not permitted. In the control group, the dose of concomitant psychotropic medications was not changed during the trial. Clinical assessments were undertaken at baseline and after 8 weeks.

It has been stated that short-term clinical trials in which patients undergo cognitive assessments with short intervals are particularly vulnerable to the effect

Table 2. Use of concomitant medications at endpoint

	First-episode group ($n=20$)		Control group ($n=10$)	
Concomitant medications	*n*	Mean daily dose (range) (mg/day)	*n*	Mean daily dose (range) (mg/day)
Anticholinergics	5	0.80 (1.0–2.0)[a]	7	1.70 (1.0–7.0)[a]
	5 (biperiden)		6 (biperiden)	
			1 (biperiden and promethazine)	
Daytime benzodiazepines	9	1.00 (0.4–7.2)[b]	4	0.88 (1.0–3.0)[b]
Hypnotics	2	0.12 (1.2)[b]	3	0.96 (1.2–4.8)[b]
Mood stabilizers			1 (carbamazepine)	600
			1 (lithium)	400
			1 (valproic acid)	600

[a]Biperiden-equivalent dose.
[b]Lorazepam-equivalent dose.

Copyright © 2012 John Wiley & Sons, Ltd.

of repeated exposure to the tests and/or assessment environment (i.e., retest effects) (Crespo-Facorro *et al.*, 2009; Goldberg *et al.*, 2010). To compare the retest effect on cognitive assessments, the control group was assessed at baseline and 8 weeks after the initial assessment. Treatment adherence was assessed by interview at each testing session.

Cognitive function, subjective quality of life, and clinical assessment

The primary outcome measure was the change in cognitive function from baseline to endpoint during blonanserin treatment. Secondary outcome measures were changes in psychiatric symptoms, subjective QOL, and severity of psychopathology.

Cognitive function was assessed by trained psychiatrists or psychologists using the Brief Assessment of Cognition in Schizophrenia—Japanese language version (BACS-J) (Kaneda *et al.*, 2007). The BACS-J has established reliability and validity and is designed to measure cognitive function in schizophrenia (Keefe *et al.*, 2004; Kaneda *et al.*, 2007). The BACS-J cognitive battery uses the following assessments in the respective targeted domains: list learning (verbal memory), digit sequencing task (working memory), token motor task (motor speed), category fluency and letter fluency (verbal fluency), symbol coding (attention and processing speed), and the Tower of London test (executive function). To reduce retest effects, subjects were randomized to receive either version A or B of the BACS-J at baseline and the other version at the endpoint session. For each assessment, a *z*-score was calculated using the mean raw scores and SD in pooled healthy controls ($n = 340$) from another study (Kaneda *et al.*, 2008).

Subjective QOL was assessed by the Schizophrenia Quality of Life Scale—Japanese language version (SQLS-J) (Kaneda *et al.*, 2002). The SQLS-J is a practical method of measuring self-reported QOL in people with schizophrenia and has established reliability and validity (Wilkinson *et al.*, 2000; Kaneda *et al.*, 2002). The 30 items on the SQLS-J are classified into three areas: (i) psychosocial conditions; (ii) motivation/energy; and (iii) symptoms/side effects. Each area scale was transformed to range from 0 (the best status) to 100 (the worst status). The "psychosocial conditions" area addresses various emotional conditions such as loneliness, hopelessness, difficulty in social situations, and worries about the future. The "motivation/energy" area addresses various problems of motivation and activity, such as the lack of will or drive to do things. The "symptoms/side effects" area addresses issues such as muscle twitches and dry mouth, which can be caused by medication (Wilkinson *et al.*, 2000; Kaneda *et al.*, 2002).

Other clinical evaluations were made by trained psychiatrists using the Positive and Negative Syndrome Scale (PANSS) (Kay *et al.*, 1987) and the Clinical Global Impression—Severity of Illness Scale (CGI-S) (Guy, 1976). Drug-induced EPS were assessed using the Drug-induced Extrapyramidal Symptoms Scale (DIEPSS) (Inada, 1996). The raters (S. M., S. O, and T. T.) were experienced clinicians who were extensively trained in the administration of outcome measures, including the PANSS and DIEPSS, before the beginning of the study to a minimum intraclass correlation of 0.80. The clinicians and psychologists who provided the clinical ratings were blinded to the assigned procedure of study patients.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 17.0 (SPSS Japan Inc., Tokyo, Japan). Differences between the first-episode group and the control group in demographic and baseline characteristics were assessed using independent sample *t*-tests, except for gender, which was assessed using the chi-squared test.

The primary aim of this study was to clarify the effects of blonanserin on cognitive function, as measured by BACS-J. A repeated measures analysis of covariance (ANCOVA) was performed for each cognitive variable with baseline data as covariate. For the primary analysis, the between-subject factor was the group (first-episode group and control group) and the within-subject factor was the time (baseline and endpoint). Effects of group, time, and group-by-time (interaction effect) were examined. Greenhouse–Geisser corrections were used when the assumption of sphericity was violated. Our main interest in the repeated measures ANCOVA was whether the group-by-time interaction reached significance for each cognitive variable. We also used a Bonferroni correction for multiple comparisons of BACS-J data. In a secondary analysis, within-group improvements in cognitive performance over time were evaluated using paired *t*-tests. Effect size (Cohen's *d*) was calculated as the within-group differences between the means divided by the pooled SD. In a third analysis, paired *t*-tests were used to assess changes in each SQLS-J subscale and other clinical assessment scores. Finally, Pearson's exploratory correlational analysis was used to determine potential associations between cognitive and clinical change scores. All statistical tests were two-tailed, and a *p*-value less than 0.05 was considered significant.

Copyright © 2012 John Wiley & Sons, Ltd.

RESULTS

Demographic and clinical characteristics

A total of 24 first-episode patients were recruited and tested at baseline. Of these, 20 (10 male and 10 female) completed the study. The reasons for drop-out were unwillingness to undergo treatment at baseline ($n=2$), loss to follow-up at week 4 ($n=1$), and transfer to another hospital at week 4 ($n=1$). In the control group, 10 were retested on the cognitive measures after 8 weeks. Thus, data from these 20 patients in the first-episode group and 10 patients in the control group were used for a completer analysis. Two patients participated as inpatients, and they moved from inpatient to outpatient status during the study. The duration of hospitalization was 13 days for a patient in the first-episode group and 34 days for a patient in the control group. The DSM-IV-TR diagnostic distribution of the participating schizophrenic patients was paranoid type ($n=19$ in the first-episode group; $n=9$ in the control group), disorganized type ($n=1$ in the first-episode group), and schizoaffective disorder ($n=1$ in the control group).

Baseline demographic and clinical characteristics of subjects are shown in Table 1. There were no significant group differences in gender, age, education level, duration of untreated psychosis that was defined as the interval between the first onset of psychotic symptoms and the administration of the first adequate antipsychotic treatment (Larsen *et al.*, 1996), or each PANSS score (all $p>0.05$). In the control group, mean duration of illness was 76.8 (±59.7; SD) months and mean duration of treatment with blonanserin was 27.1 (± 43.1) months. One patient in the control group had participated in a phase III clinical trial of blonanserin and a subsequent long-term follow-up study.

Dosage of blonanserin and concomitant drugs

In the first-episode group, the mean daily dose of blonanserin at starting after baseline assessment and at 8 weeks was 2.9 (± 1.5) and 7.2 (± 4.0) mg/day, respectively. In the control group, the mean daily dose of blonanserin during the study was 12.8 (± 7.8) mg/day. There was a significant difference between the two groups in mean dosage of blonanserin at 8 weeks ($t=-2.62$, d.f. = 28, $p=0.008$).

In the first-episode group, none of the patients had taken anticholinergics at baseline, but six patients had taken daytime benzodiazepines (mean lorazepam-equivalent dose: 0.7 [±1.7] mg/day) at baseline. Concomitant psychotropic medications used at endpoint are shown in Table 2. The difference between the two groups in mean dosage of anticholinergics (biperiden equivalents) at 8 weeks was not significant ($p>0.05$). Furthermore, the difference between the two groups in mean dosage of daytime benzodiazepines or hypnotics (lorazepam equivalents) at 8 weeks was not significant ($p>0.05$). None of the patients in either group had taken antidepressants.

Effect of blonanserin on cognitive function

Results of the BACS-J raw scores and z-scores at baseline and endpoint are shown in Table 3. Results of repeated measures ANCOVAs comparing the two groups in BACS-J z-scores are shown in Table 4. The analysis of between-group differences demonstrated no significant group effects for each BACS-J item (all $p>0.05$). The analysis of within-group differences also demonstrated no significant time effects for each BACS-J item (all $p>0.05$). Group-by-time interaction reached significance in the letter fluency task ($F=8.42$; d.f. = 1, 27; $p=0.007$), which remained so even after Bonferroni correction.

Results of paired t-tests demonstrated that z-scores of the letter fluency score and the Tower of London score were significantly increased after treatment with blonanserin in the first-episode group (all $p<0.05$) (Table 3). The effect sizes for these changes were in a moderate range (Table 3). No BACS-J subscale scores showed a significant change in the control group during the 8-week interval (all $p>0.05$).

Effect of blonanserin on other clinical assessments

Results of paired t-tests comparing changes in scores on the secondary measures from baseline to endpoint in the first-episode group are shown in Table 5. Significant improvements were found in all items on the PANSS, SQLS-J, and CGI-S (all $p<0.01$). There was a significant difference in the DIEPSS total score between baseline and endpoint in the first-episode group ($p<0.05$). Eleven patients (55.0%) in the first-episode group showed mild EPS during the study, and five patients (25.0%) required administration of low-dose anticholinergic biperiden (Table 2). There were no significant differences in each PANSS score between baseline and endpoint in the control group (Table 6).

Associations between cognitive test scores and changes in clinical assessments

There was a significant correlation between the changes in the z-score of the letter fluency task and motivation/energy score on the SQLS-J (correlation coefficient = −0.55; $p=0.041$). There were no significant correlations between changes in any of the other BACS-J scales and the PANSS, SQLS-J, CGI-S, or DIEPSS scores (all $p>0.05$). Also, there were no

Copyright © 2012 John Wiley & Sons, Ltd.

Table 3. BACS-J raw score and *z*-score at baseline and endpoint

		Baseline				Endpoint							
		First-episode group ($n=20$)		Control group ($n=10$)		First-episode group ($n=20$)				Control group ($n=10$)			
						Change		Within-group differences		Change		Within-group differences	
BACS-J[a]	Range of raw score	Raw score	*z*-score	Raw score	*z*-score	Raw score	*z*-score	Effect size[b]	p[c]	Raw score	*z*-score	Effect size[b]	p[c]
Verbal memory	0–75	41.10 (13.50)	−1.32 (1.68)	43.80 (10.61)	−0.87 (1.12)	1.85 (11.25)	0.22 (0.33)	0.15	0.48	1.80 (8.26)	0.21 (0.08)	0.46	0.28
Digit sequencing task	0–28	19.65 (3.44)	−0.62(0.90)	17.40 (4.38)	−1.27 (1.18)	−0.50 (4.49)	−0.13 (0.32)	0.12	0.61	0.90 (1.97)	0.24 (0.06)	0.30	0.31
Token motor task	0–100	60.10 (20.80)	−2.66 (1.88)	58.00 (17.61)	−3.06 (1.57)	−1.55 (10.52)	−0.14 (0.20)	0.08	0.53	2.00 (10.54)	0.21 (0.06)	0.02	0.94
Category fluency	0–	17.25 (5.48)	−0.66 (0.65)	16.40 (4.62)	−0.70 (0.50)	0.80 (4.69)	0.15 (0.16)	0.24	0.15	0.20 (2.49)	0.03 (0.11)	0.48	0.10
Letter fluency	0–	19.45 (7.55)	−1.06 (1.10)	22.20 (7.69)	−0.62 (1.05)	4.20 (1.05)	0.61 (0.10)	0.58	0.001	−1.00 (3.97)	−0.13 (0.28)	0.05	0.81
Symbol coding[d]	0–110	56.00 (13.83)	−1.12 (0.91)	46.50 (13.95)	−2.01 (1.17)	−1.30 (10.05)	−0.66 (1.44)	0.33	0.22	3.90 (5.78)	0.34 (0.06)	0.21	0.19
Tower of London	0–22	16.20 (2.57)	−1.05 (1.09)	16.40 (3.31)	−0.94 (1.40)	0.85 (2.78)	0.61 (0.18)	0.62	0.004	1.00 (3.13)	0.46 (0.62)	0.10	0.74

BACS-J, Brief Assessment of Cognition in Schizophrenia—Japanese language version.
[a]Values are mean (SD).
[b]Cohen's *d*.
[c]Paired *t*-tests were used to compare changes in *z*-score.
[d]$p < 0.05$, independent sample *t*-tests at baseline.

Copyright © 2012 John Wiley & Sons, Ltd.

Hum. Psychopharmacol Clin Exp 2012; **27**: 90–100.
DOI: 10.1002/hup