5-HT subtypes	Mode of actions	Compounds
5-HT_{1A}	(partial) agonist	tandospirone, buspirone F15599, ziprasidone aripiprazole, perospirone lurasidone
5-HT_{2A}	antagonist	clozapine, risperidone olanzapine, perospirone quetiapine, melperone N-desmethylclozapine
5-HT_6	antagonist	Ro04-6790 Lu AE58054
5-HT_7	antagonist	SB25874 amisulpiride lurasidone

Ref) Harvey et al. 2011; Kern et al. 2006; Llado-Pelfort et al. 2010, 2011; Meltzer et al. 2011; Meltzer and Massey 2011; Newman-Tancredi 2011, in press; Sumiyoshi et al. 2000, 2001a, 2001b, 2006, 2007a, 2007b, 2008, 2009

Table 1. Serotonin (5-HT) receptors in the treatment of cognitive disturbances

4. Role for 5-HT_{1A} stimulation in cognitive enhancement

The interest in the 5-HT_{1A} receptor in relation to cognition in schizophrenia was founded by a series of pilot studies of the effects of augmentation therapy with tandospirone, a 5-HT_{1A} partial agonist, in patients treated with antipsychotic drugs (Sumiyoshi T. et al. 2000, Sumiyoshi T. et al. 2001a, Sumiyoshi T. et al. 2001b). The addition of tandospirone (30 mg/day), but not placebo, to typical antipsychotic drugs (mainly haloperidol) for 4–6 weeks, was found to improve verbal memory (effect size = 0.70), memory organization, and executive function (0.63) (Sumiyoshi T. et al. 2000, Sumiyoshi T. et al. 2001a, Sumiyoshi T. et al. 2001b).

The beneficial effect of augmentation therapy with 5-HT_{1A} agonists in schizophrenia was further supported by a randomly assigned placebo-controlled double-blind study with buspirone, another 5-HT_{1A} partial agonist (Sumiyoshi T. et al. 2007a). Patients with schizophrenia, who had been treated with an atypical antipsychotic drug, were assigned to receive either buspirone, 30 mg/day, or matching placebo for 6 months. Buspirone outperformed placebo in improving the performance on a measure of attention/speeded motor performance (effect size = 0.32), indicating an advantage for cognitive abilities regulated by prefrontal cortex, as in the case of tandospirone. Evidence from these proof-of-concept studies has prompted the recent endeavor to develop cognition-enhancing drugs with 5-HT_{1A} agonist actions (Depoortere et al. 2010, Llado-Pelfort et al. 2010, Llado-Pelfort et al. 2011, Newman-Tancredi 2010, Newman-Tancredi and Kleven 2011, Newman-Tancredi and Albert in press). Some of the compounds so far synthesized in this line are shown in Fig 5.

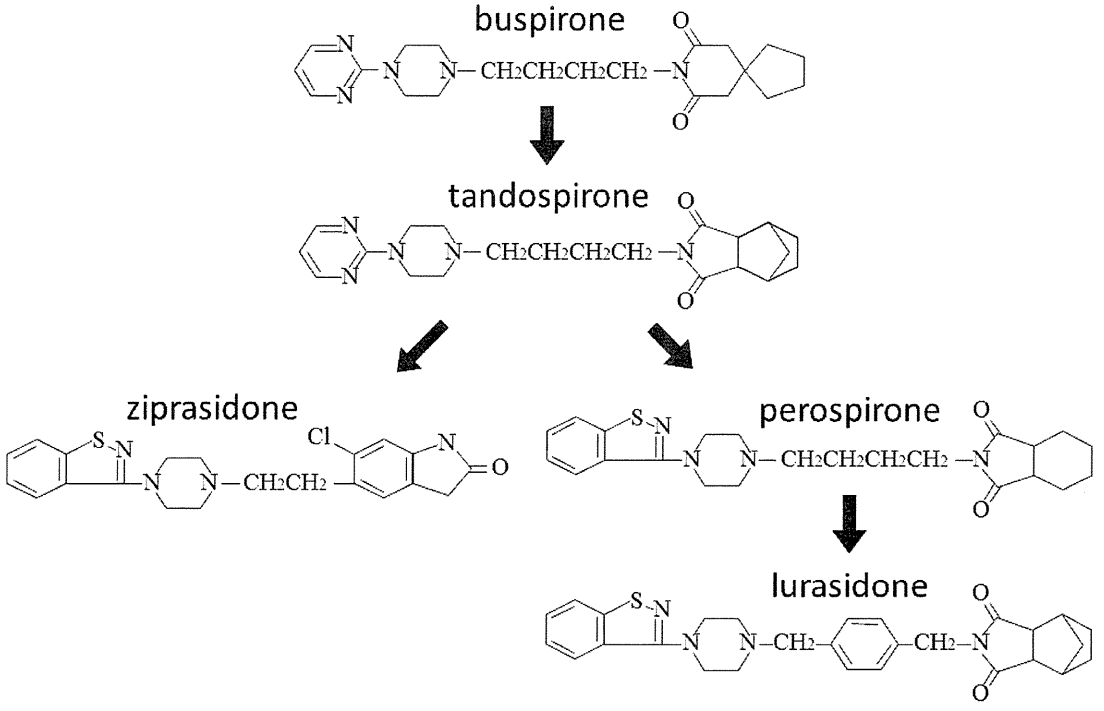


Fig. 5. Some of the psychotropic/antipsychotic compounds with agonist actions on 5-HT_{1A} receptors

Support for this therapeutic strategy comes from animal data suggesting 5-HT_{1A} partial agonists (e.g. tandospirone) and AAPDs with agonist actions on 5-HT_{1A} receptors (e.g. perospirone, aripiprazole, ziprasidone, lurasidone) ameliorate memory deficits due to NMDA receptor blockade (Hagiwara et al. 2008, Horiguchi et al. 2011, Meltzer et al. 2011, Nagai et al. 2009). The ability of these compounds to improve cognition has been related to enhancement of extracellular concentration of DA in the PFC (Bortolozzi et al. 2010, Diaz-Mataix et al. 2005, Ichikawa et al. 2001, Yoshino et al. 2004), an effect which is absent in mutant mice lacking 5-HT_{1A} (Bortolozzi et al. 2010, Diaz-Mataix et al. 2005), but not 5-HT_{2A} (Bortolozzi et al. 2010) receptors.

As illustrated in Fig. 6, Glu, GABA, 5-HT, and DA neurons constitute a network in the PFC that regulates several domains of cognition, e.g. some types of memory, executive function and attention. Among the variety of relevant receptors in this neural cascade, 5-HT_{1A} receptors are located on Glu (pyramidal) and GABA neurons. Excitation of pyramidal neurons projecting to ventral tegmental area enhances mesocortical DA function, leading to amelioration of negative and cognitive symptoms of schizophrenia (Llado-Pelfort et al. 2010, Llado-Pelfort et al. 2011). Specifically, systemic administration of 8-OH-DPAT, a prototypical 5-HT_{1A} agonist, to rats increased the discharge rate of pyramidal neurons in mPFC, by inhibiting fast-spiking GABAergic interneurons through a preferential action on 5-HT_{1A} receptors on these latter neurons (Llado-Pelfort et al. 2011). This finding reconciles

the observations that endogenous 5-HT inhibits pyramidal neurons in mPFC, while systemic administration of 5-HT_{1A} agonists excites them. These considerations are consistent with the clinical observation that augmentation therapy with tandospirone enhanced mismatch negativity, an electrophysiological cognitive marker of Glu neuron activity, in schizophrenia (Higuchi et al. 2010).

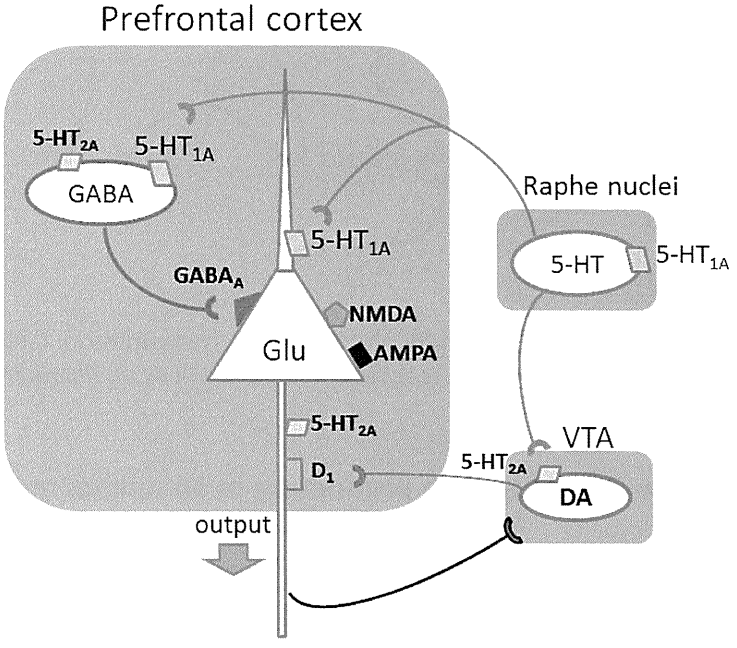


Fig. 6. Neural network in the prefrontal cortex involving glutamate, GABA, 5-HT and DA neurons. Part of the effect of 5-HT_{1A} agonists on cognition and negative symptoms is thought to be mediated by 5-HT_{1A} receptors located on GABAergic interneurons regulating glutamatergic pyramidal neurons. VTA, ventral tegmental area.

5. Lactate in brain energy metabolism

Although glucose has been considered to be a major supplier of energy in the brain, recent investigations report that lactate also plays a significant role in energy metabolism, especially during acute neural activation (Aubert et al. 2005, O'Brien et al. 2007). According to the "astrocyte-neuron lactate shuttle hypothesis" (Laughton et al. 2007, Pellerin 2003), lactate is produced in a neural activity-dependent and glutamate-mediated manner by astrocytes, and is transferred to and used by active neurons (reviewed in Uehara et al. 2008) (Fig. 7). Data from a recent study (Wyss et al. 2011) suggest that the brain prefers lactate over glucose as an energy substrate when both are available, and that lactate exerts a direct neuroprotective effect.

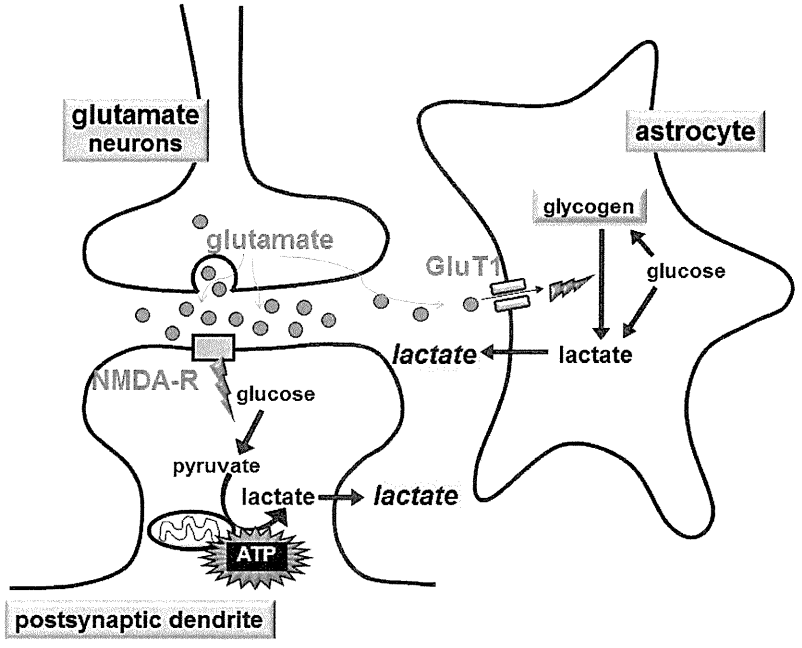


Fig. 7. Enhancement of lactate production by glutamatergic transmission. GluT1, glutamate transporter; NMDA-R, N-methyl-D-aspartate receptor. (Uehara et al. *Pharmacol Biochem Behav* 90:273, 2008)

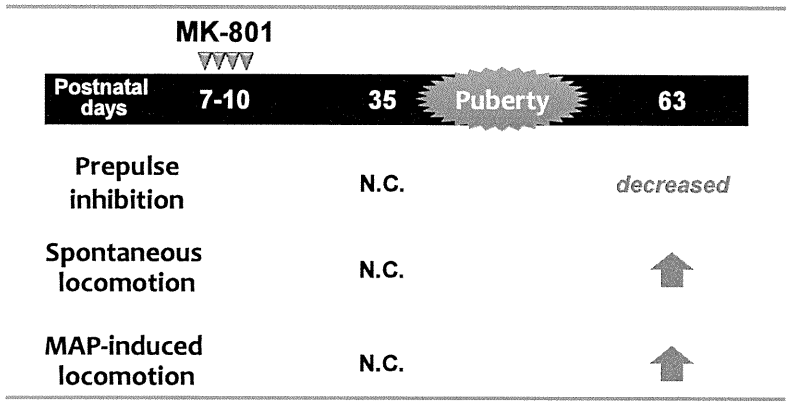
6. Role for 5-HT$_{1A}$ agonism in lactate production in an animal model of schizophrenia

Rats administered MK-801 on postnatal days (PD) 7-10 have been shown to elicit impairment of set-shifting test, a measure of prefrontal cortex function, in early adulthood (Stefani and Moghaddam 2005). The same model animals elicit disruption of prepulse inhibition, a measure of sensorimotor gating (Uehara et al. 2009, Uehara et al. 2010) and enhancement of spontaneous and metamphetamine-induced locomotor activity (Uehara et al. 2010) after, but not before puberty (Table 2). These findings suggest that transient blockade of NMDA receptors at the neonatal stage produces cognitive abnormalities in rodent models of schizophrenia based on the neurodevelopmental hypothesis of the illness.

Lactate metabolism in mPFC has been shown to be modulated by 5-HT$_{1A}$ receptors both during resting condition and acute neural activation. In particular, acute administration of tandospirone led to a significant increase in extracellular lactate concentrations, and reduced the footshock stress-induced lactate increment in the mPFC in rats (Uehara et al. 2006). Taken together, it was hypothesized that transient blockade of NMDA receptors during the neonatal stage (modeling schizophrenia) would inhibit energy demands in response to stress in the mPFC at the young adult stage, and that 5-HT$_{1A}$ partial agonist, such as tandospirone, would reverse the effect of the neonatal insult on energy metabolism.

Female Wistar rats obtained at 14 days of pregnancy. At postnatal (PD) day 7 (PD7), male pups were randomly divided into two groups. They received MK-801 (dizocilpine), or an

equal volume of saline (control; vehicle group) once daily for 4 days. At the time of weaning on PD 21, the pups were grouped into four to six per treatment.



Transient blockade of NMDA receptors by MK-801 at the neonatal stage produces disruption of prepulse inhibition, as well as spontaneous or methamphetamine (MAP)-induced hyperlocomotion after, but not before.
N.C., no change.

Table 2. Behavioral changes in a rat model of schizophrenia based on the neurodevelopmental hypothesis.

On PD49, animals were assigned to receive either saline or tandospirone at 1.0 mg/kg, (s.c.). This yielded the following groups: saline-saline group, saline-tandospirone group, MK801-saline group, and MK801-tandospirone group. For 14 days before the microdialysis examination, saline or tandospirone was administered (s.c.) once daily. Microdialysis was performed 24 hours after the last injection.

Microdialysis experiments were performed on PD63. Forty-two to 48 hr before microdialysis experiments, the animals were anesthetized, and were mounted on a stereotaxic apparatus. A dialysis probe was implanted into the left mPFC with the coordinates of A 3.2mm, L 0.6mm, V 5.2mm from bregma. The dialysis experiment was carried out on the freely moving rats. Artificial CSF was perfused into the dialysis probe. The dialysates were mixed on-line with an enzyme solution containing L-lactate dehydrogenate and NAD+ in a T-tube. During transport of the mixture to the fluorometer, lactate was enzymatically oxidized and the fluorescence of the nicotinamid adenosine dinucleotide diphosphate (NADH) formed was continuously measured, with a standard solution of 100 μmol/L lactate for calibration.

Footshock stress was administered using a plastic communication box, according to the method described previously (Uehara et al., 2006). The box (L 51cm x W 51cm x H 40cm) was equipped with a grid floor, and was subdivided into nine compartments (17cm x17cm) by transparent plastic walls. In this study, we used 4 compartments area (34cm x 34cm) for the field of free moving and footshock administration. The communication box was connected to a shock-generator to deliver footshocks as described below. Each footshock session consisted of a scramble shock of 0.3 mA for 5 seconds administered every 30 seconds for 10 minutes. After the experimental sessions, the position of dialysis probes was verified by dissection of the brain.

Data were analyzed by analysis of variance (ANOVA). The average of extracellular lactate concentrations during the period preceding the start of footshock stress (ten measurements performed every 2 min) was used as the control value (100 %). Data from tandospirone administration experiments were analyzed using three-way repeated measures ANOVA; Status and Drug were treated as between-group variables. Time was treated as a repeated measures variable.

As expected, transient neonatal administration of MK-801 suppressed lactate increment in response to footshock stress around puberty, which was reversed by 14-day treatment with tandospirone (Fig. 8). Further, the ability of tandospirone to ameliorate the response of lactate production in model animals was abolished by co-administration of WAY-100635, a selective 5-HT_{1A} antagonist (Uehara et al., in press).

These findings are consistent with clinical observations that perospirone and tandospirone improved cognitive abilities governed by the PFC, coupled with enhancement of electrophysiological activities in this brain region, in patients with schizophrenia (Higuchi et al. 2010, Sumiyoshi T. et al. 2009). This kind of translational approach is expected to provide a novel insight into the development of therapeutics targeting cognitive disturbances of schizophrenia.

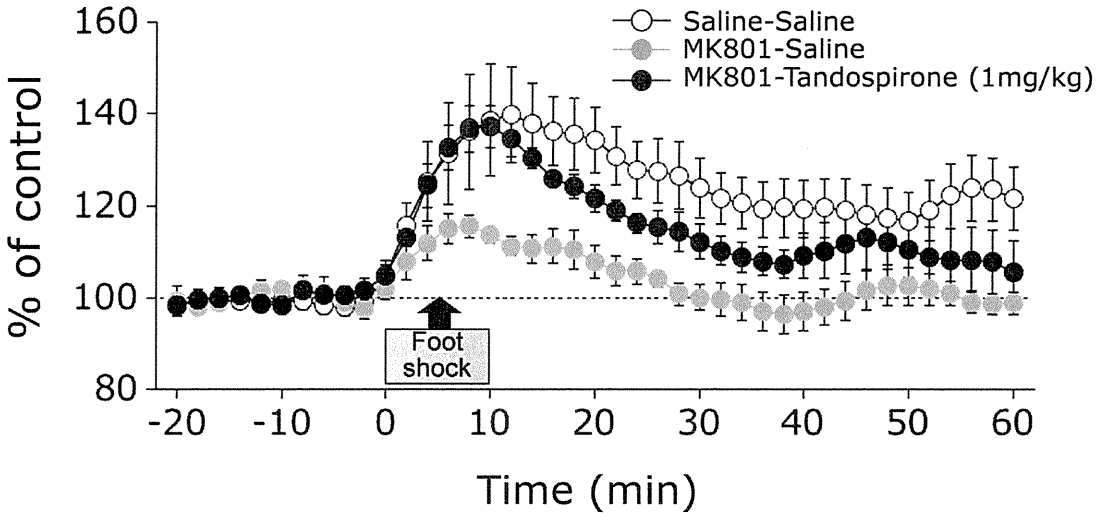


Fig. 8. Extracellular concentrations of lactate in the medial prefrontal cortex in young adult rats. Transient blockade of NMDA receptors by MK-801 at the neonatal stage (modeling schizophrenia) suppresses lactate increment in response to footshock stress (saline-saline vs. MK-801-saline). Treatment with tandospirone, a 5-HT_{1A} partial agonist, for 14 days reverses the decrease in lactate production in the model animals (MK-801-saline vs. MK801-tandospirone. A significant main effect of tandospirone in MK-801-treated animals was noted ($F(1,8)=12.94$, $P=0.007$ by ANOVA).

7. Conclusions

Behavioral, neurochemical and electrophysiological data indicate 5-HT_{1A} agonists improve negative symptoms and cognitive deficits of schizophrenia. Specifically, compelling evidence suggests that the cognitive benefits of 5-HT_{1A} agonism are mediated by Glu and

GABA neurons (Higuchi et al. 2010, Llado-Pelfort et al. 2011). The role for 5-HT_{1A} receptors in cognitive enhancement has been suggested by imaging genetics data regarding brain energy metabolism (Sumiyoshi T. et al. 2008) and by pharmacogenetics investigations (Sumiyoshi T. et al. 2010) [reviewed in (Newman-Tancredi and Kleven 2011, Newman-Tancredi and Albert in press)]. Findings from translational research, herein presented, are expected to facilitate the development of novel therapeutics for cognitive impairment in schizophrenia and other psychiatric disorders.

8. Acknowledgement

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Criterion and Construct Validity of the CogState Schizophrenia Battery in Japanese Patients with Schizophrenia

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Abstract

Background: The CogState Schizophrenia Battery (CSB), a computerized cognitive battery, covers all the same cognitive domains as the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery but is briefer to conduct. The aim of the present study was to evaluate the criterion and construct validity of the Japanese language version of the CSB (CSB-J) in Japanese patients with schizophrenia.

Methodology/Principal Findings: Forty Japanese patients with schizophrenia and 40 Japanese healthy controls with matching age, gender, and premorbid intelligence quotient were enrolled. The CSB-J and the Brief Assessment of Cognition in Schizophrenia, Japanese-language version (BACS-J) were performed once. The structure of the CSB-J was also evaluated by a factor analysis. Similar to the BACS-J, the CSB-J was sensitive to cognitive impairment in Japanese patients with schizophrenia. Furthermore, there was a significant positive correlation between the CSB-J composite score and the BACS-J composite score. A factor analysis showed a three-factor model consisting of memory, speed, and social cognition factors.

Conclusions/Significance: This study suggests that the CSB-J is a useful and rapid automatically administered computerized battery for assessing broad cognitive domains in Japanese patients with schizophrenia.

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Competing Interests: The authors have the following competing interests: Drs. Darby and Maruff are employees of CogState Ltd which developed Cogstate Schizophrenia Battery. There are no patents, products in development or marketed products to declare. This does not alter our adherence to all the PLoS ONE policies on sharing data and materials, as detailed online in the guide for authors. Dr. Kenji Hashimoto is a member of editorial Board of PLOS ONE. All other authors have declared that no competing interests exist.

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Introduction

Cognitive impairment, a core symptom of schizophrenia, is present at illness onset and usually persists even when psychotic symptoms have been successfully treated [1,2]. Furthermore, cognitive impairment is highly related to functional outcome in patients with schizophrenia [3,4]. Therefore, treatment of cognitive impairment is currently an important focus for psychopharmacology [5–10].

In contrast, the lack of an accepted standard battery for measuring cognitive impairment in patients with schizophrenia had been a major obstacle to regulatory approval of cognition-enhancing treatments. Currently, National Institute of Mental Health - Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative - Consensus Cognitive Battery (MCCB) is available for the measurement of cognitive changes in patients with schizophrenia [11,12]. The MCCB has seven domains of cognitive function, including verbal learning, speed of processing, attention/vigilance, working memory, visual learning, reasoning and problem solving, and social cognition [11]. The MCCB was approved by Food and Drug

Administration for use in clinical trials for cognitive improvement in schizophrenia [13]. However, a Japanese version of the MCCB is not yet available. In contrast, the Japanese language version of the Brief Assessment of Cognition in Schizophrenia (BACS) [14,15] has been used to measure cognitive impairments in Japanese patients with schizophrenia.

Like the BACS, the CogState Schizophrenia Battery (CSB) has been developed to provide a briefer standardized assessment of cognition in schizophrenia. Although the BACS includes only four of the seven cognitive domains of the MATRICS initiative [16,17], the CSB includes all the seven cognitive domains [18,19]. Formal validation studies have shown the CSB to have very good sensitivity to cognitive impairment in patients with chronic schizophrenia, and require approximately 40 min for administration [18,19]. There is also a strong correlation between the composite scores from the CSB and the MCCB measures in patients with schizophrenia. Furthermore, both composite scores also correlate strongly with scores on Performance-Based Skills Assessment [19]. Importantly, because the CSB was developed specifically for the measurement of cognitive change the component tasks show minimal practice effects with repeated assessment, even during very brief re-test intervals [19].

The aim of the current study is to assess the validity of the Japanese language version of the CSB (CSB-J) in Japanese patients with schizophrenia by comparing performance on this battery to that of the Japanese language version of the BACS (BACS-J) already validated for use in Japan.

Methods

Subjects

Forty patients with schizophrenia were recruited at Chiba University Hospital (Chiba, Japan), The University of Tokyo Hospital (Tokyo, Japan), National Center Hospital, National Center of Neurology and Psychiatry (Tokyo, Japan), Toyama University Hospital (Toyama, Japan), and Tokushima University Hospital (Tokushima, Japan). All patients met the DSM-IV criteria for schizophrenia. No patient had received electroconvulsive therapy. There were no specific medication criteria for inclusion in the patient group. Twenty-five of 40 patients were treated with a single second-generation antipsychotic medication (risperidone, n = 8; aripiprazole, n = 7; olanzapine, n = 6; perospirone, n = 3; quetiapine, n = 1), four patients were treated with a single first-generation antipsychotic (haloperidol, n = 1; fluphenazine, n = 1; bromperidol, n = 1; sulpiride, n = 1), nine patients were treated with a combination of antipsychotic drugs (aripiprazole and quetiapine, n = 2; risperidone and quetiapine, n = 1; risperidone and haloperidol, n = 1; risperidone and levomepromazine, n = 1; haloperidol and levomepromazine, n = 1; haloperidol and zotepine, n = 1; risperidone, haloperidol, and bromperidol, n = 1; risperidone, haloperidol, and zotepine, n = 1), and two patients were medication free. Only two female patients were inpatients.

Forty healthy controls were recruited at the same five sites. They were screened with the Structured Clinical Interview for DSM-IV Axis I Disorders, Non-Patient Edition and were required not to have an Axis I disorder according to DSM-IV criteria. None had a first-degree family history of schizophrenia or schizoaffective disorder.

Inclusion criteria for all subjects in both groups included proficiency in Japanese language, normal or corrected-to-normal visual function, and at least a 9th-grade education. Exclusion criteria for all subjects in both groups included any current or past histories of neurological disorders (other than schizophrenia for the patient group), including head injury, cerebral vascular disorders, epilepsy, or alcohol or drug use disorders. No subject was treated with donepezil. Participants who had severe symptoms of depression (defined by the Japanese version of the Calgary Depression Scale for Schizophrenia (JCDSS) [20,21] score of more than 9) were excluded from the study. Smokers were excluded because nicotine and nicotine withdrawal might have effects on cognition.

Study investigators made a concerted effort to recruit healthy controls who would match the patients on age, male/female ratio, and premorbid intelligence quotient (IQ) as assessed by the Japanese Adult Reading Scale-25 words version (JART-25) [22], which is Japanese version of National Adult Reading Test. Age was considered the primary demographic variable of interest since it was likely to have the greatest impact on cognition. The 40 subjects of both groups were divided into 4 age groups (1, 20–29 years old; 2, 30–39 years old; 3, 40–49 years old; 4, 50–65 years old). Prior to commencement of the study, all subjects provided written informed consent after receiving a full explanation regarding the nature of the study and potential risks and benefits of study participation. The study was approved by the relevant ethics committee of each institute and performed in accordance with the Declaration of Helsinki II. The ethics committees of each institute were: the Ethics Committee of Chiba University Graduate School of Medicine (Chiba, Japan), the Ethical Committee of the Faculty of Medicine, University of Tokyo (Tokyo, Japan), the Ethics Committee of National Center of Neurology and Psychiatry (Tokyo, Japan), the Committee on Medical Ethics of Toyama Medical and Pharmaceutical University (Toyama, Japan), and the Ethics Committee of University of Tokushima (Tokushima, Japan).

Assessment procedures

All subjects completed two batteries of cognitive tests administered by trained psychiatrists or psychologists. All subjects received the CSB-J followed by the BACS-J version A. JART-25 was completed after the BACS-J. All subjects were tested in a single day. In addition, the Positive and Negative Syndrome Scale (PANSS) [23] was completed along with the BACS-J. Short breaks of five minutes or less were provided as needed throughout testing. Subjects were instructed to avoid caffeine in all forms from 20 minutes prior to assessments to the end of all tests.

The CSB-J consists of eight tasks that measure verbal learning (International Shopping List Task; ISLT), speed of processing (Detection Task; DET), attention/vigilance (Identification Task; IDN), visual working memory (One Back Task; ONB), visual memory (One Card Learning Task; OCL), spatial working memory (Continuous Paired Association Learning Task; CPAL), reasoning and problem solving (Groton Maze Learning Task; GML), and social cognition (Social Emotional Cognition Task; SECT). The primary measure from each task of the CSB-J was standardized by creating Z-scores whereby healthy control mean was set to zero and the standard deviation set to one, following the methodological procedure used by Keefe et al. [14]. A composite score was calculated by averaging all Z-scores of the eight primary measures from the CSB-J. In this study, we used the original version of the CSB with a slight modification. First, the Two Back Task was omitted to reduce test duration because we considered the ONB sufficient to assess working memory function [19]. Second, the CPAL can provide another non-verbal paired associate learning [24]. Third, the list of words in the ISLT was customized for the study as recommended by the authors to match regional Japanese culture and minimize cross-cultural test bias [25]. Fourth, stimuli in the SECT were also customized to only

include faces with a Mongoloid countenance to avoid any other-race effects that can occur on tasks that use representations of human faces [26].

The CSB-J data were uploaded to a secure account on the CogState server (http://www.cogstate.com). Uploaded outcome parameters were calculated using custom software blind to diagnosis. Logarithmic and arcsine transformations for speed and accuracy measures respectively were performed in order to avoid violation of necessary statistical preconditions. A description of the battery's administration and the eight cognitive tasks has been reported previously for non-Japanese subjects [19,27].

Data analysis

Student's t-test and Fisher's exact test were used to examine differences between groups. For the analysis of concurrent validity, Pearson product-moment correlations were computed between scores on subtests of the CSB-J and the BACS-J within each cognitive domain. Stepwise General Linear Models (GLM) with the CSB-J composite score or subscores as the dependent variable were conducted. At first, with combined patients' and controls' data, GLM were used to evaluate the effects of the following independent variables on cognitive performance: age, sex, premorbid IQ, education, JCDSS score. Second, with patients' data, GLM were used to evaluate the effects of the following independent variables on cognitive performance: age, gender, premorbid IQ, illness duration, duration of untreated psychosis (DUP), the dosage of antipsychotic medication, the dosage of anticholinergic medication, PANSS positive syndrome scale score, PANSS negative syndrome scale score, PANSS general psychopathology scale score. The structure of the CSB-J was determined by performing the Maximum Likelihood extraction methods with oblique rotation. The Kruskal-Wallis test was used to compare cognitive impairment among different subtypes of schizophrenia. Values of $p<0.05$ were considered to indicate statistical significance.

Results

Demographic data and clinical variables

Demographic and clinical variables are presented in Table 1. Age, gender, estimated premorbid IQ and education did not differ for the two groups. The JCDSS score in patients was significantly higher than that of healthy controls, indicating that the schizophrenia patients group suffered more depressive symptoms.

Missing data across all sessions and administration time

The total amount of missing data across all tasks within the CSB-J was 1.25%. The reason for missing data was the time restriction of each subtest of the CSB-J. There was no missing data for the BACS-J subtests. The total administration time of the CSB-J (51.1±12.2 min (mean ± SD)) was significantly ($t=10.719$, $p<0.001$) longer than that of the BACS-J (35.6±4.4 min (mean ± SD)).

Validity and stepwise analysis

Figure 1 and 2 shows the performance of patients on each of the primary measures and composite score of the CSB-J and the BACS-J compared to the healthy control, respectively. Significant differences in scores between the patients and the controls were observed for all of the subtests of the CSB-J and the BACS-J.

The CSB-J composite score was significantly correlated with the BACS-J composite score ($r=0.709$; $p<0.001$ for patients, $r=0.483$; $p<0.01$ for controls; $r=0.760$; $p<0.001$ for total subjects) as shown in Table 2 and Figure 3. Stepwise GLM showed that age and premorbid IQ were independent predictors of the CSB-J composite scores. Lower cognitive performance was associated with increased age and lower premorbid IQ. After accounting for age and premorbid IQ, the difference between both composite scores remained. Other clinical variables were not correlated with the CSB-J composite score.

Next, we examined correlations between corresponding subtests from the CSB-J and the BACS-J. Because the BACS-J includes only four of the seven cognitive domains selected by the MATRICS initiative, we examined correlations of corresponding subtests in only these four domains. ISLT score and DET score were significantly correlated with the BACS-J verbal memory score ($r=0.725$, $p<0.001$) and the BACS-J symbol coding score ($r=0.466$, $p<0.01$) in patients, respectively. There were no significant correlations between other corresponding subtests (Table 2).

Furthermore, we examined the effect of five subtypes of schizophrenia on the CSB-J scores in patients with schizophrenia although the number of each subtype was small. The CSB-J score in each subtype is shown in Table S1. The disorganized subtype (n = 3) demonstrated intact cognition. The paranoid subtype (n = 20) and the catatonic subtype (n = 4) performed significantly worse on ISLT and the CSB-J composite score than controls. The undifferentiated subtype (n = 4) performed significantly worse on ISLT, IDN, and composite score than controls. The residual subtype (n = 9) performed significantly worse on broader domains than controls, and had stronger impairment on the CSB-J composite score (Figure 4 and Table S1).

Factor analysis of the CSB-J subtests

In a factor analysis of the CSB-J, the eigenvalue-greater-than-one rule and scree plot converged on a three-factor solution that accounted for 53.8% of the total variance. The Kaiser-Mayer-Olkin measure was calculated at 0.587 and Bartlett's test of sphericity was significant at $p<0.001$. The factor loadings are presented in Table 3. Subtests that needed memory loaded on Factor 1, including CPAL, OCL, ISLT, and GML. Subtests that needed speed loaded on Factor 2, including DET and IDN. The SECT loaded on Factor 3. The ONB was not associated with this three-factor solution.

Discussion

The present study is the first one to report the use of a complete MCCB compatible battery in Japanese schizophrenia patients and shows that the CSB-J is a useful neuropsychological battery for assessing global cognitive impairment in Japanese patients with schizophrenia. The CSB-J was easy to use and well tolerated by patients with a 98.8% completion rate and acceptable administration time with mean of 51.1 minutes. Although the administration time of the CSB-J was about 15 minutes longer than that of the partial MCCB BACS-J battery (with average of 35.6 minutes administration duration), the difference was probably in part because the CSB-J covered more cognitive domains than the BACS-J. In addition, there was a significant correlation between the CSB-J and the BACS-J composite scores in both the patients with schizophrenia and healthy control subjects groups, consistent with the previous results using the original English version of the CSB and standardized tests and the MCCB [18,19].

The results of this study also provide evidence of good construct validity for verbal memory and attentional domains between the CSB-J and BACS-J tasks, which are considered to evaluate these abilities. In particular, the ISLT and DET scores of the CSB-J were significantly correlated with the verbal memory and the

Table 1. Demographic and symptom information.

	Controls (n = 40)	Patients (n = 40)	*p*-value
Age (years)	39.6±11.9 (22–59)	39.6±12.3 (22–65)	1.000
Male/Female	20/20	20/20	1.000
Premorbid IQ	107.1±8.5 (89–120)	103.7±10.1 (79–120)	0.114
Education (years)	15.0±1.8 (12–20)	14.3±2.0 (10–20)	0.139
JCDSS	0.6±1.4 (0–6)	2.2±2.4 (0–9)	0.001
Illness duration (years)		15.6±11.6 (2–38)	
Duration of untreated psychosis (years)		2.5±6.0 (0–37)	
Chlorpromazine equivalents (mg)		410.8±305.6 (0–1250)	
Biperiden equivalents (mg)		1.0±1.9 (0–6)	
PANSS positive		14.1±5.2 (6–24)	
PANSS negative		17.9±6.1 (9–36)	
PANSS general		33.1±10.9 (18–47)	

Data are the mean ± S.D. Parenthesis is the range.
JCDSS: the Japanese version of Calgary Depression Scale for Schizophrenia.
PANSS: Positive and Negative Syndrome Scale.
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symbol coding scores of the BACS-J in patients, respectively. However, there were no significant correlations between the other subscores of the CSB-J and the corresponding subscores of the BACS-J that are considered to evaluate speed of processing, working memory, and reasoning and problem solving. These differences presumably relate to different task requirements. For example, the BACS-J token motor test requires an ability to coordinate both hands simultaneously, whilst the CSB-J IDN task requires simpler motor abilities for pushing the response buttons. Prior good correlations for the IDN task and information processing speed measures have been reported in non-Japanese schizophrenic patients [18], and a poor correlation between the token motor test and a corresponding conventional test [14,28], suggest that these tests measure differing abilities. Likewise, verbal fluency is associated with multiple cognitive abilities, including speed of processing, reasoning ability and other aspects of executive function such as inhibition [29]. Similarly, the tasks evaluating working memory from the different batteries had significant differences. The ONB and CPAL tasks using the CSB-J probably correlate with visual and spatial working memory, whilst the digit sequencing of the BACS-J may correlate less with visual and more with verbal working memory. With respect to reasoning and problem solving, although both the GML task of the CSB-J and the Tower of London from the BACS-J require planning, inhibition, and working memory, the latter has been considered more of a planning task [30], whereas the GML task appears to highlight spatial working memory abilities [31]. Differences between the constructs evaluated by these two batteries appear a more salient explanation for the lack of correlations, since both the CSB-J subtests and the BACS-J subtests have been reported to be significantly correlated with the corresponding standard battery subscores [15,19].

The factor analysis performed on the CSB-J suggests that three factors of cognitive performance can be derived from the CSB-J scores. The first factor had memory as a common ability and included the CPAL, OCL, ISLT, and GML tasks. A second speed

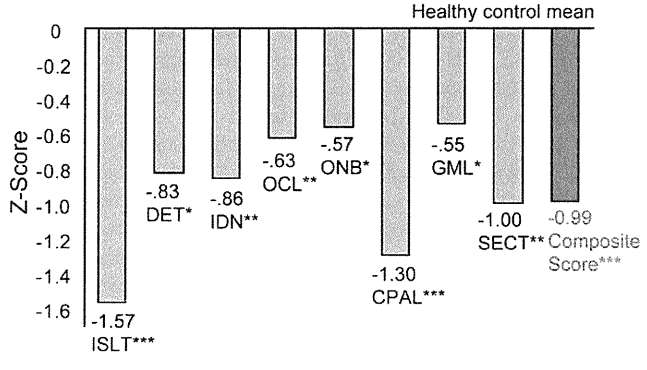

Figure 1. Magnitude of impairment relative to matched healthy controls on each cognitive measure from the CSB-J. Abbreviation: ISLT International Shopping List Task, DET Detection Task, IDN Identification Task, OCL One Card Learning Task, ONB One Back Task, CPAL Continuous Paired Association Task, GML Groton Maze Learning Task. Numbers of the figure are Z-score. *$p<0.05$, **$p<0.01$, ***$p<0.001$.
doi:10.1371/journal.pone.0020469.g001

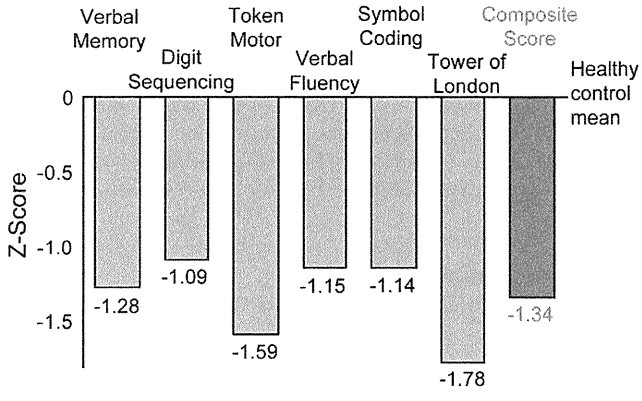

Figure 2. Magnitude of impairment relative to matched healthy controls on each cognitive measure from the BACS-J. Numbers of the figure are Z-score. All subtests and composite score were $p<0.001$.
doi:10.1371/journal.pone.0020469.g002

Table 2. Correlation efficiencies between the CSB-J and the BACS-J for the same cognitive domains.

Cognitive domain		Patients	Controls	Totals
Verbal learning	International Shopping List Task vs. BACS-J Verbal memory	.725***	.424**	.714***
Speed of processing	Detection Task vs. BACS-J Token motor	.105	.025	.207
	Detection Task vs. BACS-J Verbal fluency	−.184	−.031	−.003
	Detection Task vs. BACS-J Symbol coding	.466**	−.167	.341**
Working memory	One back Task vs. BACS-J Digit sequencing	.169	−.041	.181
	Continuous Paired Association Task vs. BACS-J Digit sequencing	.192	.284	.342**
Reasoning and problem solving	Groton Maze Learning Task vs. BACS-J Tower of London	.135	.276	.250*
Composite Score	The CSB-J Composite Score vs. The BACS-J Composite Score	.709***	.483**	.760***

*$p<0.05$,
**$p<0.01$,
***$p<0.001$.
doi:10.1371/journal.pone.0020469.t002

of performance factor included the DET and IDN tasks, and a third factor separated out the SECT task, which includes abilities collectively considered important in social cognition. It has been suggested that social cognition represents a separate cognitive domain in schizophrenia [32]. Social cognitive ability is considered to be an important predictor of effective social [33] and community function (including interpersonal relationships and work functioning) independent of abilities in other cognitive domains [34,35]; however we did not perform additional social and community functional assessments in this study. Taken together, the CSB-J may have an advantage over the BACS-J because the BACS-J lacks a social cognition subtest.

Although the numbers of each diagnostic subtype of schizophrenia were small in this study, we did find that each subtype had a quite different profile of CSB-J score. Both the undifferentiated subtype and the residual subtype had major cognitive impairment on the CSB-J composite score, consistent with previous reports [36,37]. In contrast, Brazo et al. [38] reported that the disorganized subtype had major cognitive impairments, whereas in our study the disorganized subtype had intact cognitive function. The reasons underlying this discrepancy are currently unknown. Clearly a larger sample will be required to further investigate this issue.

There are some limitations of this study. First, some subtests of the CSB-J were not assessed in the criterion-related validity analysis. This is because of the absence of equivalent MCCB domain specific tests for Japanese. Second, the assessment of social cognition by emotional perception alone does not cover many of the putative abilities thought to underlie this complex behavior. Further studies will be required if other social and emotional cognitive tasks are adapted for Japanese patients. Third, the sample size of this study was small (n = 40 for each group), and larger studies would aid in confirming and extending the findings of the current study. Further detailed studies of the CSB-J in comparison to a complete Japanese language version of the MCCB and other social cognitive abilities such as theory of mind and attributional style would help determine the applicability of this promising battery. Furthermore, the current study did not repeat the batteries precluding assessment of test-retest validity, which is considered by the MATRICS initiative investigators a vital feature of a test battery to be used in clinical trials of schizophrenia [11]. Since test-retest results have been reported for both the CSB and the MCCB in non-Japanese control subjects and schizophrenic patients [39–41], such studies using Japanese samples are recommended.

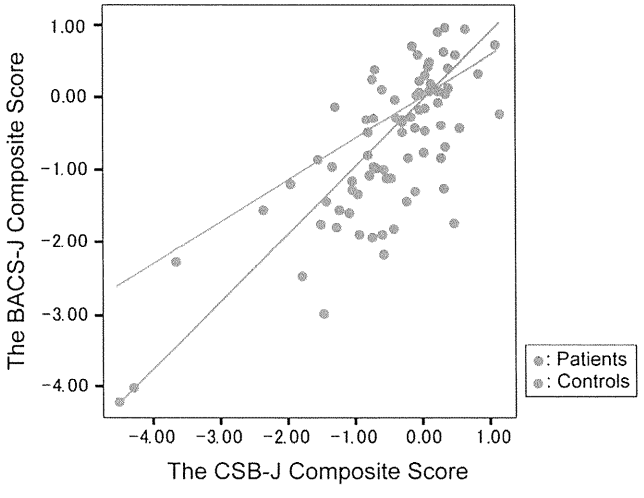

Figure 3. Inter-correlations between the CSB-J composite score and the BACS-J composite score. Controls: r = 0.483; p<0.01, Patients: r = 0.709; p<0.001, Total subjects: r = 0.760; p<0.001.
doi:10.1371/journal.pone.0020469.g003

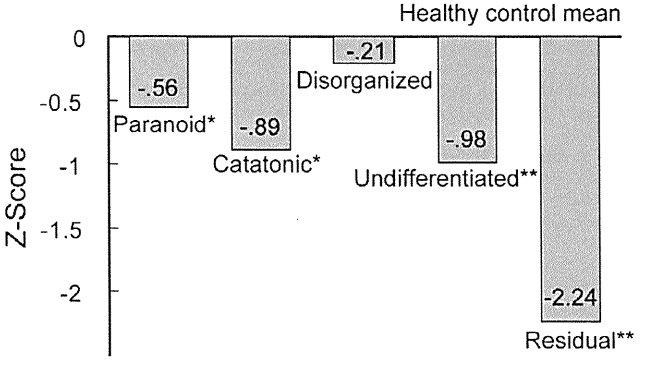

Figure 4. Effects of subtype on CSB-J composite score in patients with schizophrenia. Number of the figure is Z-score. *P<0.05, **P<0.01 as compared with control.
doi:10.1371/journal.pone.0020469.g004

Table 3. Factor loading of the CSB-J subtests in patients with schizophrenia.

	Factor 1	Factor 2	Factor 3
Continuous Paired Association Learning Task	***.912***	.028	.063
One Card Learning Task	***.552***	.006	−.211
International Shopping List Task	***.517***	−.127	−.177
Gorton Maze Learning Task	***.432***	.053	.372
Detection Task	.116	***.987***	−.136
Identification Task	−.202	***.734***	.224
Social Emotional Cognition Task	−.025	−.037	***.908***
One Back Task	−.174	.077	.365

doi:10.1371/journal.pone.0020469.t003

In conclusion, the present study showed that the CSB-J was sensitive to cognitive impairment in Japanese patients with schizophrenia, and that the CSB-J composite score was significantly correlated with the BACS-J composite score providing initial criterion and construct validation. Although further studies are required to address test-retest validity, the CSB-J appears to be a promising cognitive battery to assess the therapeutic effects on potential cognitive-enhancing agents in Japanese patients with schizophrenia.

Supporting Information

Table S1 The CSB-J subscores of each subtype of schizophrenia. *$p<0.05$, **$p<0.01$ (for post-hoc analysis). Kruskal-Wallis tests; post-hoc tests; comparison between each subtype and controls. The comparison procedure was appropriately adjusted by reducing the level of significance (Bonferroni procedure). ISLT: International Shopping List Task, DET: Detection Task, IDN: Identification Task, ONB: One Card Learning Task, CPAL: Continuous Paired Association Learning Task, GML; Gorton Maze Learning Task, SECT: Social Emotional Cognition Task.
(DOCX)

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Author Contributions

Conceived and designed the experiments: TY KT KH. Performed the experiments: TY MS KA YM TT SE CL SY M. Ishikawa YH T. Se YU MT YK M. Iyo KK TH T. Su TO. Analyzed the data: TY. Contributed reagents/materials/analysis tools: YK DD PM. Wrote the paper: TY KH. Calculated the uploaded raw data using custom software of CogState Ltd: DD PM.

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LORETA analysis of three-dimensional distribution of delta band activity in schizophrenia: Relation to negative symptoms

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ABSTRACT

We sought to determine if altered electroencephalography (EEG) activities, such as delta band activity, in specific brain regions are associated with psychotic symptoms. Data were obtained from 17 neuroleptic-naive patients with schizophrenia and age- and sex-matched 17 healthy control subjects. Low Resolution Brain Electromagnetic Tomography (LORETA) was used to generate current source density images of delta, theta, alpha, and beta activities. Localization of the difference in EEG activity between the two groups was assessed by voxel-by-voxel non-paired *t*-test of the LORETA images. Spearman's correlation coefficient was obtained to relate LORETA values of EEG current density in brain regions showing a significant between-group difference and psychopathology scores. Delta band activity, represented by LORETA current density, was greater for patients in the following areas; the left inferior temporal gyrus, right middle frontal gyrus, right superior frontal gyrus, right inferior frontal gyrus, and right parahippocampal gyrus. LORETA values for delta band activity in the above five brain regions were negatively correlated with negative, but not positive symptoms. The results of this study suggest the role for electrophysiological changes in some of the brain regions, e.g. prefrontal cortex, in the manifestation of negative symptoms.

1. Introduction

Schizophrenia is a relatively common and often debilitating neuropsychiatric disorder that develops after puberty with prevalence being approximately 0.85% throughout life. Its symptoms include positive symptoms (e.g. delusions, hallucinations, and thought disorders), negative symptoms (e.g. affective flattening, and poverty of speech), and cognitive deficits, such as impairment of memory and attention (Crow, 1980; Sumiyoshi et al., 2000).

Imaging studies have suggested functional deviations in various brain areas, especially, prefrontal cortex (Cleghorn et al., 1989; Andreasen et al., 1992, 1997; Parellada et al., 1994; Sabri et al., 1997) in subjects with schizophrenia.

Although some brain imaging methods based on blood flow or metabolism, e.g. fMRI and PET, are associated with high spatial resolution, they may not appropriately differentiate functional excitation and inhibition of neural 38 activity (Pascual-Marqui et al., 1999).

Electroencephalography (EEG) offers information with high time resolution which enables, for example, frequency analysis. However, scalp distributions of EEG power of various frequency bands are generally ambiguous (Pascual-Marqui et al., 1999), and depend on the reference sites used. Therefore, numerical analyses, such as dipole source modeling, are required to obtain precise locations of EEG generators.

Low Resolution Brain Electromagnetic Tomography (LORETA) (Pascual-Marqui et al., 1994; Pascual-Marqui, 1995) 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. With this method, brain electrical data 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 (Pizzagalli et al., 2001; Flor-Henry et al., 2004).

Abbreviations: EEG, electroencephalography; LORETA, Low Resolution Brain Electromagnetic Tomography; SAPS, the Scale for the Assessment of Positive Symptoms; SANS, the Scales for the Assessment of Negative Symptoms.

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Table 1
Demographic data of participants.

	Schizophrenia (n = 17)	Healthy controls (n = 17)
Females/Males	6/11	6/11
Age (years)	26.5 (6.4) (range, 16–38)	26.5 (4.4) (range, 18–39)
Education (years)	14.7 (2.1)	15.1 (2.4)
Age of onset (years)	24.6 (6.6)	–
Duration of illness (years)	2.00 (2.1)	–
SAPS	35.5 (27.4)	–
SANS	52.6 (14.3)	–

Values represent mean (SD) SAPS; Scale for the Assessment of Positive Symptoms SANS; Scale for the Assessment of Negative Symptoms.

A recent development of imaging technique, such as LORETA and its modified versions (e.g. sLORETA), has improved the spatial resolution of EEG and event-related potentials by providing three-dimensional distribution pattern of these electrophysiological activities (Sumiyoshi et al., 2011). Using LORETA, Pascual-Marqui et al. (1999) reported asymmetrically enhanced delta band activities in the prefrontal cortex in neuroleptic-naïve, first-episode schizophrenia. On the other hand, Mientus et al. (2002) found an increase in delta band activity, most prominently in the anterior cingulate gyrus and temporal lobes, in unmedicated patients, while other frequency activities were not altered. These results suggest that enhanced delta band activity in the prefrontal cortex is associated with the pathophysiology of schizophrenia. However, there has been, to our knowledge, no study that addressed the correlation between delta band activity and the symptomatology of schizophrenia, e.g. positive and negative symptoms, using three-dimensional imaging methods, such as LORETA.

Negative symptoms of schizophrenia have been associated with structural impairment in the prefrontal cortex, and have been hypothesized to arise from decreased dopaminergic activity in this brain region (Lynch, 1992). Using SPECT, Molina Rodriguez et al. (1997) found severity of negative symptoms was negatively correlated with the degree of prefrontal lesions. Also, decreased glucose metabolism in the frontal cortex was associated with greater negative symptoms in subjects with schizophrenia (Potkin et al., 2002; Sabri et al., 1997). These previous observations indicate a role for prefrontal cortex in the psychopathology of schizophrenia, especially negative symptoms.

Taken together, it was hypothesized that aberrant neural activity in specific brain areas, as measured by electrophysiological methods, would be associated with psychotic symptoms, especially negative symptoms. In this study, we sought to determine (1) 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, and (2) if such electrical change would be associated with negative symptoms. To our knowledge, this study was the first to address these issues in neuroleptic-naïve patients using the LORETA imaging method.

2. Method

2.1. Subjects

Data were obtained from seventeen right-handed patients (female/male = 6/11) meeting DSM-IV-R criteria for schizophrenia (APA, 1994) at Toyama University Hospital. Demographic data for these patients are shown in Table 1. All patients were neuroleptic-naïve. Diagnosis was based on the Structured Clinical Interviews for DSM-IV (SCID). Psychiatric and treatment history was obtained from the patients, informants, and medical records. Subjects with current history of substance abuse or dependence, seizure, head injury and as any other medical condition known to interfere with EEG were excluded from the study. Eligible patients had a complete physical examination. Standard laboratory testing (blood count, liver and renal function, blood sugar, total cholesterol, and triglyceride) was normal. Clinical staff explained the nature of the study to the subjects, the risks and benefits, and the option not to participate in research. If the mental status of a subject was impaired to the point where s/he could not understand the nature of the study, its risks and benefits, or the option not to participate, the subjects was not approached to be in the research. This protocol was approved be the Committee on Medical Ethics of University of Toyama. After complete description of the study to the subjects, written informed consent was obtained. Fourteen patients were outpatients who were lightly and moderately ill without hospitalization. Three patients were in-patients. Seventeen age, gender, and education-matched right-handed healthy volunteers also participated in the study as control subjects. Demographic data for these control subjects are also shown in Table 1.

2.2. Design and procedure

The Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1983b), and the Scales for the Assessment of Negative Symptoms (SANS; Andreasen, 1983a) were assessed by an experienced psychiatrist (Table 1).

Electroencephalograms (EEGs) were recorded with a 32-channel DC-amplifier (EEG-2100 version 2.22J, Nihon Kouden Corp., Tokyo, Japan). Recordings were performed using an electrocap (Electro-cap Inc., Eaton, OH) in a sound-attenuated room. The EEG was recorded with 19 electrodes located at FP1, FP2, F3, F4, F7, F8, C3, C4, P3, P4, O1, O2, T3, T4, T5, T6, Fz, Cz, and Pz according to the international 10–20 system. All electrodes were referenced to the average amplitude of ear electrodes (bandwidth = 0.16–120 Hz, 60 Hz notch Filter). Electrode impedance was less than 10 kΩ. Data were controlled with a sampling rate of 256 Hz. Recording was conducted after eye closure for 5 min.

Off-line, the data were carefully screened for eye, muscle or eye-movement, and technical artifacts. Twenty 1-s epochs were available from all participants.

LORETA is a method to localize multiple distributed cortical sources of bioelectric activity in the three-dimensional space (Pascual-Marqui et al., 1994). In other words, LORETA demonstrates the synchronously activated neuronal populations underlying EEG activity by computing their cortical localization from the scalp distribution of the electric field. The LORETA inverse solution is based on existing neuroanatomical and physiological knowledge and a mathematical constraint called the smoothness assumption (Pascual-Marqui et al., 2002). The principles of LORETA and the mathematical tools have been described in details at http://www.uzh.ch/keyinst/NewLORETA/Software/Software.htm.

In order to mathematically mitigate the disturbing effects of the electrically conducting layers between the cortical surface and the electrodes, LORETA computes the inverse solution within a three-shell spherical head model including scalp, skull, and brain. The brain compartment of this model was restricted to the cortical grey matter and hippocampus, according to the Talairach Brain Atlas digitized at Montreal Neurological Institute (Talairach and Tournoux, 1988). The grey matter compartment was subdivided in 2394 voxels, which allows a spatial resolution of 7 mm. Cross-modal validation studies disclosed that LORETA and other functional neuroimaging methods showed the same cortical localization of dysfunction in several neuropsychiatric conditions (Pascual-Marqui et al., 2002).

We investigated the LORETA solution in seven frequency bands separately: Delta (1.5–6.0 Hz), theta (6.5–8.0 Hz), alpha-1 (8.5–10.0 Hz), alpha-2 (10.5–12.0 Hz), beta-1 (12.5–18.0 Hz), beta-2 (18.5–21.0 Hz), and beta-3 (21.5–30.0 Hz) were determined (Kubicki et al., 1979).

2.3. Statistical analyses

Group comparisons with respect to age and education were performed with the unpaired t test. The localization of the differences in activity between the groups was assessed by voxel-by-voxel nonpaired t test of the LORETA images, based on the power of estimated electric current density, which results in t statistic three dimensional images (Mientus et al., 2002). In these images, cortical voxels of statistically significant differences were identified by a nonparametric approach using randomization strategy that determined the critical probability threshold values for actually observed statistic with corrections for multiple testing (Holmes et al., 1996). Test results are presented as Figs. 1 and 2; and Table 2. Figures include information about the direction of changes between tested groups, either an increase (red-colored) or a decrease (blue-colored), and provide information about the significance of changes by indicating t-values that are significant at 0.1% level. LORETA specifications claim their corrected t for $P < 0.05$ level as significant enough for testing 2394 voxels in one comparison (as used be other authors (Arai et al., 2003; Flor-Henry et al., 2004), however, a lower significance level (e.g. 5%) would have made it difficult to show the maximum areas of activation differences (Mientus et al., 2002). For all frequency bands, ROIs were chosen only for brain areas showing significant group-difference in LORETA values at 0.1% level.

Spearman's correlation coefficient was obtained to relate LORETA current density in these ROIs vs. SAPS and SANS scores. For this analysis, significance was set at 1% level for Bonferroni correction.

3. Results

Group comparisons 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 (ITG) (maximum $t = 4.27$). A significant increase in delta band activities were also found for the right middle frontal gyrus (MFG) (maximum $t = 4.26$), right inferior frontal gyrus (IFG) (maximum $t = 4.16$), right superior frontal gyrus (SFG) (maximum $t = 4.03$), and right parahippocampal gyrus (PHG) (maximum $t = 4.03$) (Table 2, Fig. 1). Further, theta and alpha-2 frequency bands showed a trend-level increase (Table 2, Fig. 2). There were no significant group differences for alpha-1, beta-1, and beta-2 frequency bands.

Next, we determined correlations between the average of LORETA current density for delta band activity in the above 5 ROIs vs. SAPS and SANS Total scores. LORETA values for delta band activity at these brain regions (Table 3, Fig. 3) were negatively correlated with the SANS Total score. Specifically, the correlation for the ITG survived even after Bonferroni correction. On the other hand, there were no significant correlations between LORETA current density for delta band activity and the SAPS score.

4. Discussion

Patients with schizophrenia demonstrated an increase in LORETA values for delta band activity at several brain areas, including those in prefrontal cortex. Moreover, the increase in delta band activity was negatively associated with overall negative symptoms.

To our knowledge, our report is the first study which examined the correlations between specific band activity based on three-dimensional distribution of EEG and negative symptoms in neuroleptic-naïve patients with first-episode schizophrenia. LORETA current source images with 19 or more electrodes have been shown to provide good estimates of the localization for activated brain regions identified with f-MRI signals (Mulert et al., 2004; Sumiyoshi et al., 2009).

Koles et al. (2004) compared LORETA current densities from 57 male patients with schizophrenia and 65 matched control subjects. Comparisons were made during resting conditions and during verbal and spatial cognitive challenges. Results indicate that, for the delta band, significant differences in current density occupied the largest brain volume during the resting condition, with bilateral frontal regions showing increased current density. For the alpha band, the differences in current density occupied the smallest brain volume during the cognitive condition with decreased current density in schizophrenia in the right frontal region. In the beta band, the differences in current density occupied large brain volumes irrespective of cognitive state with increased current source density for schizophrenia. Data from all of the band frequencies in the resting condition, presented in the current study, confirm most of the previous findings with schizophrenia.

Increased delta activity in frontal regions in patients with schizophrenia is in agreement with other quantitative EEG (QEEG) and functional neuroimaging studies (Frith, 1997; Pascual-Marqui et al., 1999; Mientus et al., 2002; Tislerova et al., 2008). The increase in LORETA current density for delta band activity in the frontal and temporolimbic-occipital cortex in subjects with schizophrenia may provide an electrophysiological basis for aberrant function of frontal cortex (Ingvar et al., 1976; Guich et al., 1989), a notion supported by neuroimaging data (Ingvar and Franzen, 1974; Weinberger, 1987; Andreasen et al., 1992; Weinberger and Berman, 1996).

Tislerova et al. (2008) found an increase in the delta and theta frequencies over the fronto-temporo-occipital cortex, particularly in the temporolimbic structures, as well as an increase in alpha-1 and alpha-2 activities in the temporal cortex in neuroleptic-naïve patients with schizophrenia compared to healthy control subjects. They also found an increase in beta-1 and beta-2 in the temporo-occipital and posterior limbic structures in these patients. Mientus et al. (2002) reported an increase in delta activity, particularly in the anterior cingulate gyrus and left temporal lobes, in patients with unmedicated schizophrenia. These previous findings are generally in agreement with our observations (Table 2, Fig. 1).

The difference in delta band activity between patients and control subjects was largest at left ITG (Table 2, Fig. 1). Meisenzahl et al. (2008) reported that patients with first-episode schizophrenia revealed reduction in the volume of the left ITG compared to healthy controls. Also, grey matter volume reductions in the bilateral ITG have been reported in first episode (Kuroki et al., 2006) and chronic (Onitsuka et al., 2004) schizophrenia. Although there is little information about the role of ITG in the psychopathology of schizophrenia, our results reported here suggest the contribution of this brain area to affective disturbances of the illness.

The increase in delta band activity in the prefrontal cortex (MFG, IFG, and SFG), presented here, is consistent with the hypofrontality (Guich et al., 1989), which typically becomes apparent under a cognitive challenge. For example, patients with schizophrenia show deficits in working memory and executive function, as revealed, for example, by the Wisconsin Card Sorting Test (Buchsbaum et al., 1990; Andreasen et al., 1992; Tamminga et al., 1992; Hazlett et al., 2000; Ragland et al., 2007). An increase in delta band activity in the PHG and prefrontal cortex may be associated with a neural basis for cognitive deficits of schizophrenia. In this context, PHG has been shown to play an important role in verbal learning memory, a key domain of cognition relevant to social outcome (Sumiyoshi et al., 2006).