Table 2
Distribution of OFC the sulcogyral pattern in schizophrenia patients and healthy controls.

	Schizophrenia (N = 72)	Controls (N = 86)	Past controls[a] (N = 100)	χ^2	p
	N (%)	*N* (%)	*N* (%)		
Left hemisphere				6.12	0.106
Type I	29 (40.3)	49 (57.0)	47 (47.0)		
Type II	11 (15.3)	12 (14.0)	35 (35.0)		
Type III	32 (44.4)	24 (28.0)	18 (18.0)		
Type IV	0 (0)	1 (1.2)	0 (0.0)		
Right hemisphere				9.76	0.021
Type I	40 (55.6)	64 (74.4)	63 (63.0)		
Type II	6 (8.3)	9 (10.5)	27 (27.0)		
Type III	25 (34.7)	13 (15.1)	10 (10.0)		
Type IV	1 (1.4)	0 (0)	0 (0.0)		

[a] Distribution of OFC pattern in previously-reported healthy controls [combined sample of Chiavaras and Petrides (2000) and Nakamura et al. (2007)] is shown here for reference.

replicated inter-individual variability in the OFC sulcogyral pattern in healthy subjects and alteration in its distribution in schizophrenia. Given that the OFC H-shaped sulcus develops predominantly during the gestational period from 28 to 44 weeks (Chi et al., 1977; Kringelbach and Rolls, 2004), the present and previous MRI findings suggest neurodevelopmental insults, such as impairment of axon elongation in the OFC (Sekiguchi et al., 2011), occur during the mid-late gestational period in schizophrenia. It is hypothesized that such an early neurodevelopmental lesion renders the brain vulnerable to anomalous post-pubertal neurodevelopmental processes, as indicated by evidence for accelerated gray matter loss and aberrant connectivity particularly in prefrontal regions, and that these anomalous neurodevelopmental processes interact with other causative factors associated with the onset of psychosis (e.g., stress or other environmental factors) (Pantelis et al., 2005).

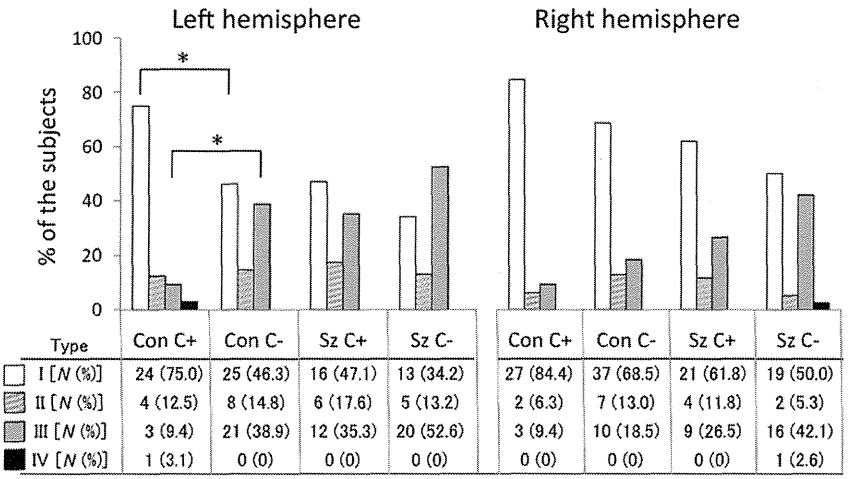
One major finding of this study was the significant effect of the *YWHAE* genotype on the left OFC sulcogyral pattern, especially for healthy subjects. *YWHAE* is a gene encoding 14-3-3epsilon, one of the *DISC1*-interacting molecules that play a crucial role in neuronal development via transport of the NudE-like (*NUDEL*)/lissencephaly-1 (*LIS1*) complex (Taya et al., 2007; Toyo-oka et al., 2003). The exact mechanism of development of the OFC sulcogyral pattern remains unclear, but the gross cortical folding pattern in human brains is strongly regulated by genetic factors (Bartley et al., 1997; Gregorio et al., 2009) and likely reflects critical neurodevelopmental events, such as neuronal migration, local neuronal connection, and synaptic development (Armstrong et al., 1995; Rakic, 1988). Several MRI studies in mono- and dizygotic twins support the notion that cortical folding is also influenced by non-genetic factors (Hasan et al., 2011; Zilles et al., 2013). However, taken together with animal data that genetically modified 14-3-3epsilon-deficient mice showed decreased dendritic spine density and impairment of the local neuronal network in the OFC (Sekiguchi et al., 2011), our results suggest that the genotype variation of 14-3-3epsilon could significantly affect the processes involved in neuronal development related to cortical folding patterns in the orbitofrontal region. Furthermore, the significant relation between the Type I pattern and protective C allele of *YWHAE* in this study may partly support the hypothesis by Bartholomeusz et al. (2013) that the Type I pattern is associated with more efficient neural organization in the OFC, and this may potentially be linked to better axonal connectivity with other brain regions and more efficient processing.

Table 3
Distribution of the OFC sulcogyral pattern in subjects with and without the *YWHAE C allele*.

	C allele carriers (N = 66)	*G* homozygotes (N = 92)	χ^2	p
	N (%)	N (%)		
Left hemisphere			9.49	0.024
Type I	40 (60.6)	38 (41.3)		
Type II	10 (15.2)	13 (14.1)		
Type III	15 (22.7)	41 (44.6)		
Type IV	1 (1.5)	0 (0)		
Right hemisphere			3.18	0.365
Type I	48 (72.7)	56 (60.9)		
Type II	6 (9.1)	9 (9.8)		
Type III	12 (18.2)	26 (28.3)		
Type IV	0 (0)	1 (1.1)		

On the other hand, we did not find a genotype effect of *YWHAE* on the OFC pattern specific to schizophrenia, although genetic and expression evidence (Ikeda et al., 2008), as well as animal studies (Ikeda et al., 2008; Sekiguchi et al., 2011), have implicated its role as a susceptibility gene related to the prefrontal pathology of schizophrenia (Goldman-Rakic, 1994). Several MRI studies have demonstrated that individuals at increased genetic risk of schizophrenia at least partly share abnormal frontal cortical folding, including an altered OFC pattern (Chakirova et al., 2010), with patients with schizophrenia (Falkai et al., 2007; Harris et al., 2004, 2007; Jou et al., 2005). Furthermore, the structural stability of cortical folding is generally archived soon after birth (Armstrong et al., 1995) and is independent of regional volumetric changes (Nakamura et al., 2008; Takayanagi et al., 2010), whereas dynamic brain changes, including excessive cortical thinning (van Haren et al., 2011) or gray matter reduction (Mane et al., 2009) over time in the frontal area, may occur during early phases of schizophrenia (Pantelis et al., 2007). All of this neuroimaging evidence implies that disturbed frontal gyrification may represent a static endophenotypic risk marker of schizophrenia. The current findings suggest that the *YWHAE* genotype effect alone is not likely to explain the altered OFC sulcogyral pattern in schizophrenia. However, given that schizophrenia is a heterogeneous disorder with a multifactorial etiology (Harrison and Weinberger, 2005; Sawa and Snyder, 2002), further analyses of *DISC1*-related and other susceptibility genes, as well as their interactions, will be required to clarify the molecular basis related to the neurodevelopmental pathology of schizophrenia.

A few possible confounding factors in this study should be taken into account. First, we examined only a single polymorphism in one of the *DISC1*-interacting molecules in a relatively small sample. Although we found a significant *YWHAE* genotype effect only on the left OFC sulcogyral pattern in healthy subjects, a non-significant but similar effect of the protective C allele (increased Type I and decreased Type III expression) was also observed in schizophrenia (Fig. 2). Thus, the potential role of genetic variation in *DISC1*-interacting molecules and their interaction with other genetic/non-genetic factors should be further tested in larger cohorts. Second, the current study cannot address the disease specificity of our OFC findings. An altered orbitofrontal sulcogyral pattern (increase of Type III) has been also reported in autism spectrum disorders (Watanabe et al., in press) and a genome-wide analysis has shown that specific SNPs are associated with a range of psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium and Genetic Risk Outcome of Psychosis, GROUP Consortium, 2013). Finally, we examined schizophrenia patients with an



Type	Con C+	Con C-	Sz C+	Sz C-	Con C+	Con C-	Sz C+	Sz C-
I [N (%)]	24 (75.0)	25 (46.3)	16 (47.1)	13 (34.2)	27 (84.4)	37 (68.5)	21 (61.8)	19 (50.0)
II [N (%)]	4 (12.5)	8 (14.8)	6 (17.6)	5 (13.2)	2 (6.3)	7 (13.0)	4 (11.8)	2 (5.3)
III [N (%)]	3 (9.4)	21 (38.9)	12 (35.3)	20 (52.6)	3 (9.4)	10 (18.5)	9 (26.5)	16 (42.1)
IV [N (%)]	1 (3.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.6)

Fig. 2. Distribution of the orbitofrontal sulcogyral pattern in each diagnostic group. C+, subjects with C allele; C−, subjects without C allele; Con, controls; Sz, schizophrenia. *$p < 0.01$.

illness duration of approximately 5 years in this study. Illness chronicity (Haijma et al., 2013) and medication with antipsychotics (Andreasen et al., 2013; Lieberman et al., 2005; Moncrieff and Leo, 2010) can significantly affect brain morphology. Although there was no difference in these variables between the patients with and without the C allele (Table 1) and gross cortical folding patterns remain rather stable throughout life in healthy subjects (Armstrong et al., 1995; Magnotta et al., 1999), the present findings should be replicated using patients at early illness stages and in un-medicated patients.

5. Conclusion

The present study replicated an altered sulcogyral pattern of the OFC in schizophrenia and further suggested that genotype variation in *YWHAE* may be related to the development of cortical folding patterns in the orbitofrontal region. Although we did not observe a genotype effect of *YWHAE* on the OFC pattern specific to schizophrenia, our findings support the possible role of the OFC sulcogyral pattern as an endophenotype for future genetic studies of schizophrenia.

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Brief report

Olfactory sulcus morphology in established bipolar affective disorder

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ABSTRACT

This MRI study examined the morphology of the olfactory sulcus, a potential marker of early neurodevelopment in 26 patients with bipolar I disorder and 24 matched controls. Bipolar patients had significantly shallower olfactory sulci bilaterally compared to controls, suggesting that neurodevelopmental abnormalities contribute to the neurobiology of bipolar disorder.

1. Introduction

A large number of studies suggest a close relationship between olfactory and affective information processing, with common underlying neural substrates including limbic structures (Soudry et al., 2011). Although olfactory function in bipolar disorder (BD) has not been well documented (Burón and Bulbena, 2013), several recent studies have demonstrated olfactory dysfunction in BD (Cumming et al., 2011; Hardy et al., 2012; Lahera et al., in press) or in a BD subgroup with psychotic symptoms (Striebel et al., 1999).

The olfactory sulcus appears during fetal development at around 16 weeks of gestation (Chi et al., 1977), and its depth has been related to olfactory function in healthy subjects (Hummel et al., 2003). For psychiatric disorders, an abnormally shallow olfactory sulcus has been reported in schizophrenia (Turetsky et al., 2009a; Takahashi et al., 2013), supporting the notion that olfactory dysfunction is a prominent feature of schizophrenia and may represent a marker of early neurodevelopmental abnormalities (Brewer et al., 2001; Turetsky et al., 2009b; Kamath et al., 2014). In addition to clinical and biological commonality between BD and schizophrenia (Whalley et al., 2012; Tamminga et al., 2013), some neuroimaging (e.g., Takahashi et al. (2010)) and post-mortem studies suggest a possible embryonic developmental etiology also in BD (reviewed by Sanches et al. (2008)). Furthermore, BD patients and their unaffected first-degree relatives are likely to share brain morphologic changes related to olfactory processing (e.g., anterior-limbic structures) (Matsuo et al., 2012; Nery et al., 2013), suggesting that abnormalities in the olfactory structures may be at least partly associated with vulnerability to BD. It remains largely unknown, however, whether BD patients exhibit morphologic changes of the olfactory sulcus.

This magnetic resonance imaging (MRI) study investigated the olfactory sulcus morphology in BD patients and matched controls. Based on previous olfactory ability findings in BD and the potential role of olfactory sulcus depth as a marker of early neurodevelopment, we predicted a shallower olfactory sulcus in BD patients compared with controls. We also investigated the association between olfactory sulcus morphology and clinical features of BD.

2. Methods

2.1. Participants

Twenty-six patients with DSM-IV bipolar I disorder and 24 age- and gender-matched healthy controls participated in this study (Table 1). Patients were recruited through advertisement and via a dedicated specialist bipolar disorder clinic based in Sydney, Australia. Diagnoses were made by a research psychiatrist (GM) using the Structured Clinical Interview for DSM-IV (SCID-IV-P) (First et al., 1998), supplemented by case note review. The majority of patients were euthymic at the time of scanning. Controls were recruited predominantly via advertisement, and they were screened for a personal and family history of psychiatric or neurological disorder using the SCID-IV nonpatient version (SCID-NP). Participants were right-handed and excluded if they had a history of ongoing substance misuse,

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Table 1
Sample characteristics and olfactory sulcus measures.

Variable	Healthy controls (N =24)	Bipolar patients (N =26)	Group comparison
Age (years)	38.7 ± 11.1	38.4 ± 10.9	ANOVA: $F(1,48)=0.01$, $P=0.928$
Male/female	7/17	8/18	Chi-square=0.02, $P=0.902$
NART-estimated IQ[a]	115.1 ± 9.6	113.8 ± 7.1	ANOVA: $F(1,47)=0.28$, $P=0.597$
Education (years)	14.6 ± 2.1	14.7 ± 2.8	ANOVA: $F(1,48)=0.02$, $P=0.899$
Illness duration (years)	–	13.5 ± 10.1	–
Number of manic episodes	–	8.8 ± 10.2	–
Number of depressive episodes	–	11.1 ± 10.8	–
Lithium dosage (mg, $N=12$)	–	975 ± 213	–
Valproate dosage (mg, $N=12$)	–	1437 ± 594	–
Intracranial volume (cm^3)	1461 ± 148	1476 ± 126	ANCOVA[b]: $F(1,47)=0.13$, $P=0.715$
Olfactory sulcus length (mm)			ANCOVA: $F(1,44) < 0.01$, $P=0.988$
Left	43.9 ± 4.7	44.1 ± 4.3	
Right	44.7 ± 4.7[c]	45.4 ± 3.8[c]	
Olfactory sulcus depth (mm)			ANCOVA: $F(1,44) = 51.55$, $P < 0.001$
Left	12.4 ± 1.2[d]	10.6 ± 0.8	
Right	13.6 ± 1.3[d,e]	11.4 ± 1.0[e]	

Data are presented as mean ± SD.
ANCOVA, analysis of covariance; ANOVA, analysis of variance; IQ, intelligence quotient; NART, National Adult Reading Test.

[a] Data missing for one bipolar patient.
[b] Age was used as a covariate.
[c] $P=0.007$: longer than in left hemisphere (post hoc Scheffé's test).
[d] $P<0.001$: deeper than in bipolar patients (post hoc Scheffé's test).
[e] $P<0.001$:deeper than in left hemisphere (post hoc Scheffé's test).

neurological disease or, in patients, if there was a co-morbid Axis I or II DSM-IV diagnosis that required treatment. All participants gave written informed consent and the local Hospital and University ethics committee approved the study.

At the time of scanning, eight patients were taking lithium, seven were taking valproate, and four were taking a combination of both. One patient was taking valproate and carbamazepine, and another was taking carbamazepine alone, while five patients were medication free. All patients had previously been exposed to antipsychotic medication, although none within 12 months of entering the study. Ten patients had a family history of major affective disorders (bipolar disorder, $N=3$; unipolar depression, $N=5$; and both, $N=2$), while 12 had no family history of affective disorders and four had an unknown family history. Sixteen patients had a history of psychosis (hallucinations and/or delusions) during at least one affective episode.

2.2. MRI procedures

T1-weighted MR scans were acquired with a 1.5-T GE Signa scanner. Imaging parameters were as follows: echo time, 5.3 ms; repetition time, 12.2 ms; field of view, 24.9 cm; voxel dimensions, 0.98 × 0.98 × 1.6 mm thick coronal slices. The intracranial volume (ICV) was measured as previously described (Eritaia et al., 2000); the groups did not differ in their ICVs (Table 1).

For the assessment of the olfactory sulcus, the images were processed on a Linux PC using Dr. View software (AJS, Tokyo, Japan). Brain images were realigned in three dimensions and reconstructed into contiguous coronal images with a 0.98-mm thickness, perpendicular to the anterior commissure-posterior commissure line. As described in detail elsewhere (Takahashi et al., 2013), one rater (TT), who was blind to the subjects' identity, measured the depth of the olfactory sulcus in all coronal slices where the sulcus was clearly seen. On each coronal slice, the olfactory sulcus was traced beginning with the deepest point of the sulcus and ending inferiorly with a tangent line connecting the top surfaces of the gyrus rectus and medial orbital gyrus (Rombaux et al., 2009) (Fig. 1). The length of the sulcus in the anterior-posterior direction (mm) was determined by the multiplication of the number of these coronal slices by 0.98. Intra- and inter-rater (TT and YN) intraclass correlation coefficients for the length and depth of the sulcus in 10 randomly selected brains were over 0.8.

2.3. Statistical analysis

The average depth (sum of the depth in all slices containing the sulcus/slice number) and length of the olfactory sulcus were analyzed using repeated measures analysis of covariance (ANCOVA), with age and ICV as covariates, diagnosis and gender as between-subject factors, and hemisphere as a within-subject variable. The sulcus morphology of the patient subgroups (psychotic and nonpsychotic, with and without a family history, with and without lithium or valproate treatment at scanning) was also analyzed by ANCOVA, covarying for age and ICV. Post-hoc Scheffé's tests were used.

The relationships between the olfactory sulcus measures and clinical variables were examined using Pearson's partial correlation coefficients controlling for age and ICV. The number of manic/depressive episodes was log-transformed because of their skewed distribution. Statistical significance was defined as $P<0.05$.

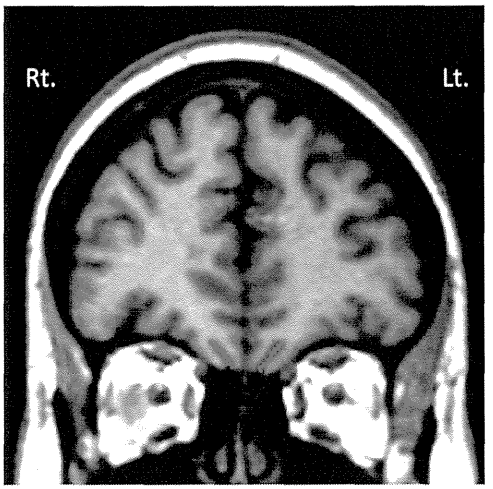

Fig. 1. T1 coronal image of the olfactory sulcus at the level of PPTE (posterior tangent through the eyeballs).

3. Results

ANCOVA of the sulcus depth revealed significant main effects for diagnosis [$F(1, 44)=51.55$, $P<0.001$] and hemisphere [$F(1, 46)=83.14$, $P<0.001$] but no interaction between these factors; the BD patients had a shallower sulcus than controls, and the sulcus was deeper in the right than in the left hemisphere (Table 1, Fig. 2). There was no group difference in the sulcus length, but the olfactory sulcus was longer in the right hemisphere [$F(1, 46)=6.88$, $P=0.012$] (Table 1). No significant effect involving gender was found.

There were no significant differences in the sulcus measures between the patient subgroups on the basis of psychotic symptoms, family history, and lithium treatment status. The BD patients taking valproate had a longer sulcus bilaterally compared with those who were not on valproate treatment [$F(1, 22)=7.73$, $P=0.011$].

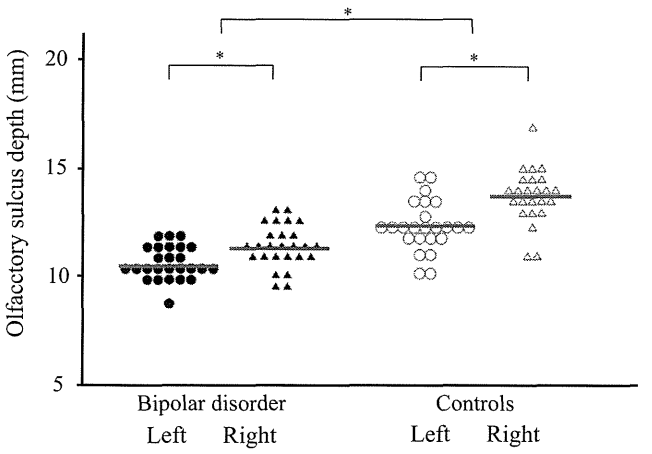

Fig. 2. Olfactory sulcus depth in the patients with bipolar disorder and healthy controls. Horizontal lines indicate mean values. Post hoc Scheffé's test: $^{*}P < 0.01$.

No significant relation was found between the olfactory sulcus measures and clinical variables in the BD patients (onset age, illness duration, number of manic/depressive episodes, dosage of lithium or valproate) after Bonferroni correction. Age, IQ, and education did not significantly correlate with the sulcus measures in either group.

4. Discussion

To our knowledge, this is the first MRI study to report the morphologic changes of the olfactory sulcus in established bipolar I disorder. The BD patients had significantly shallower olfactory sulci bilaterally compared with controls, but there was no group difference in its anterior-posterior length. Illness duration, number of affective episodes, and medication status did not affect the sulcus depth of the patients, suggesting that it might be a static illness marker reflecting abnormal neurodevelopment.

Olfactory dysfunction appears to be a promising vulnerability marker of schizophrenia (e.g., Turetsky et al. (2009b)), and early studies have reported relatively intact olfactory function in BD (Burón and Bulbena, 2013). However, several recent studies have demonstrated olfactory impairment in BD and a relationship to their affective (Cumming et al., 2011; Hardy et al., 2012) or psychotic (Striebel et al., 1999) symptomatology as well as social functioning (Hardy et al., 2012; Lahera et al., in press), which could be partly attributable to a close functional and neuroanatomical relationship between olfactory ability, emotional processing, and social cognition (Soudry et al., 2011; Lahera et al., in press). The present MRI results of abnormally shallow olfactory sulcus in BD partly support these olfactory ability findings, as this anatomical abnormality could be associated with embryonic disruption of olfactory system development (Abolmaali et al., 2002; Hummel et al., 2003). However, rather intact olfactory functioning before illness onset and its deficits in first-episode psychotic BD (Brewer et al., 2001, 2003) raise the possibility that progressive changes in olfactory functioning may occur following illness onset. Although our findings suggest a role of neurodevelopmental abnormalities in the neurobiology of BD, future longitudinal studies should examine whether the olfactory sulcus morphology remains stable in the course of BD.

Regarding the timing of neurodevelopmental abnormalities in BD, we previously demonstrated abnormally small adhesio interthalamica (Takahashi et al., 2010), which develops at a similar gestation period as the olfactory sulcus (Rosales et al., 1968), in the same BD subjects as in this study. However, these patients had normal size of the cavum septi pellucidi (Takahashi et al., 2010), which is related to fusion of the septum pellucidi within 3–6 months of birth (Shaw and Alvord, 1969), supporting the idea that BD is more closely related to aberrant neurodevelopment early in gestation.

We did not assess olfactory function or additional olfactory structures (e.g., olfactory bulb), representing a limitation of the study. Furthermore, the small sample number and heterogeneity (e.g., history of psychosis, family history of affective disorders, medication status, and number of episodes) of BD patients limited our ability to generalize the findings. Mood stabilizers may affect brain morphology (Moore et al., 2002) as well as olfactory discrimination ability (Castro et al., 2012), but comprehensive medication data (e.g., lifetime medication) were not available. Given our unexpected finding of the effect of valproate on the sulcus length, possible effects of medication as well as other possible confounding factors on olfactory sulcus morphology are worthy of further examination in larger and well-characterized BD cohorts. As olfactory deficits are also reported in other psychiatric disorders such as major depression (Burón and Bulbena, 2013), the disease specificity of our findings should be further examined.

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Review article

The future of real-world neuroscience: Imaging techniques to assess active brains in social environments

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ABSTRACT

The human brain is characterized by an evolutionarily new, highly developed neocortex, which has characteristic connections with phylogenically older structures to enable adaptation to complex social environments. Adaptive social behavior requires successful mental representations of the self and others' emotions and intentions. Measurement of brain activity under laboratory-based settings has been the gold standard in previous cognitive neuroscience studies. However, these measurement settings may be sub-optimal if we want to visualize brain function in active individuals in real-world environments. Neuroscience has historically developed through generations of the "sensing brain," "emotional brain," "social brain," and "ego brain." The next generation is the "action brain" combined with "real-world neuroscience" perspective. To enable in situ measurement of the action brain, real-world or two-person neuroimaging techniques are necessary to visualize brain dynamics during natural social situations, such as the presence of others. This review discusses recent literature describing non-human primate (NHP) and human brain functions during active behaviors in social environments. Uncovering the neurobiological mechanisms of the active brain in the presence of others by using real-world neuroimaging will be an important step toward fully understanding the human brain and its mental functions.

Contents

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1. Introduction: investigations into the active brain using next-generation real-world neuroimaging

The human brain is characterized by phylogenetically newer prefrontal and other neocortices that have evolved to realize adaptive social life (Teffer and Semendeferi, 2012). Real-world social situations require adaptive behaviors that are realized by conscious and unconscious representations, as well as future expectations of self and others' emotions and intentions. To investigate the neural mechanisms underlying such active behaviors, "real-world neuroimaging" or "two-person neuroimaging" should be developed as a novel technology to enable the visualization of brain dynamics associated with socially adaptive actions in relatively more natural settings than the laboratory. To understand how the era of the active brain using real-world neuroimaging has emerged as the next generation of neuroscience research, it is important to understand the historical perspective of brain research development.

1.1. Historical perspective of the four stages of brain research development

Human brain research that has investigated brain function from a systems neuroscience viewpoint can be categorized into four stages: the "sensing brain" era starting in late 1950s, the "emotional brain" era beginning in the late 1970s, the "social brain" era in the late 1990s, and the "ego brain" era starting in the late 2000s (Fukuda, 2008).

1.1.1. Sensing brain

The sensing brain era was mainly driven by animal studies. The neuronal mechanisms underlying vision were excellently described based on the results of cat studies that were started in 1958 by the pioneering neuroscientists D.H. Hubel and T.N. Wiesel, who were awarded the 1981 Nobel prize in physiology or medicine. Their work was followed by studies of more complicated information processing and memory by L.R. Squire and E.R. Kandel. Their sophisticated analyses resulted in major findings around 1990, and they were awarded a Nobel prize in 2000. These studies focused on intellectual aspects of input information processing; that is, objective processing of the outside world.

1.1.2. Emotional brain

The emotional brain era was also primarily driven by findings from animal studies. The important roles of the limbic system in emotion were impressively demonstrated in lengthy studies starting in late 1970s by J.E. LeDoux. His summarizing monograph "Emotional Brain" was published in 1996. Based on these studies, emotion came to be regarded as a rapid evaluation system of the biological significance of information. This role of emotion indicates subjective processing of outside world, which is in contrast to objective processing by the sensing brain. In humans, such subjective and objective processes roughly correspond to unconscious and conscious processing. This may explain why LeDoux was also interested in psychoanalysis, a subdivision of psychiatry that deals with the unconscious aspect of human mind.

1.1.3. Social brain

By necessity, the social brain era was driven by NHP and human studies because social abilities have only fully evolved in primate species. It is noteworthy that these advances were supported by technological advances in brain imaging, including functional magnetic resonance imaging (fMRI) starting in 1990. fMRI enabled in vivo brain activity measurement in humans; previous techniques such as unit neuron recording or direct brain recording methodologies were not considered appropriate for human use. Starting in the late 1990s, the neural substrates of representation of other individual minds were identified as the mirror neuron system, theory of mind system, and empathy system for motion, thoughts, and emotion, respectively. These developments have opened a new social brain era that moves past the traditional isolated brain studies to assess interpersonal relationships.

1.1.4. Ego brain

The fourth and most recent ego brain era is an extension of the social brain era that started in the late 2000s and has focused on the brain substrates of self functions in humans (ego). Topics in ego brain studies include the metacognitive aspects of one's own personality as self-referential judgment and one's own emotion as alexithymia and the motor aspect of the self as sense of agency. Because conscious and overt self functions are considered specific to humans, study of the ego brain is limited to fMRI analyses of human subjects.

1.2. The action brain as the fifth generation of neuroscience

Traditionally, studies conducted in real-world settings have multiple variables and can be affected by unexpected events; thus, they have been grouped into the category of applied sciences. Conversely, basic science studies are conducted in laboratory settings. However, when considering the most fundamental functions of the brain, surviving in the real world is more critical than providing correct responses to tests in a laboratory setting. That is, real-world life requires the brain to adapt to, alter, and survive social environments. The *action brain* deals with this essential function (Fig. 1).

Thus, the action brain is assumed to be the fifth stage of human brain research, and it can be desirably studied using real-world neuroscience methods. To date, human brain function has been examined while subjects remain motionless with minimum behavioral responses during MRI. Although they may perform social or metacognitive tasks while undergoing fMRI examinations, the obtained data should be interpreted as constrained by the unnatural, behaviorally covert, and solitary nature of examination settings. Actual brain functions can also be monitored in more natural situations during overt behaviors and communications.

The study of brain function during overt actions, especially in such real-world situations, will be the fifth stage of neuroscience research: the action brain in real-world settings. This neuroscience concept of the *action brain combined with real-world perspective* could also be termed "in situ neuroscience" and is supposed to include real social interactions ("*two-person neuroscience*"). Recently, the issue of "symbol grounding" in the fields of

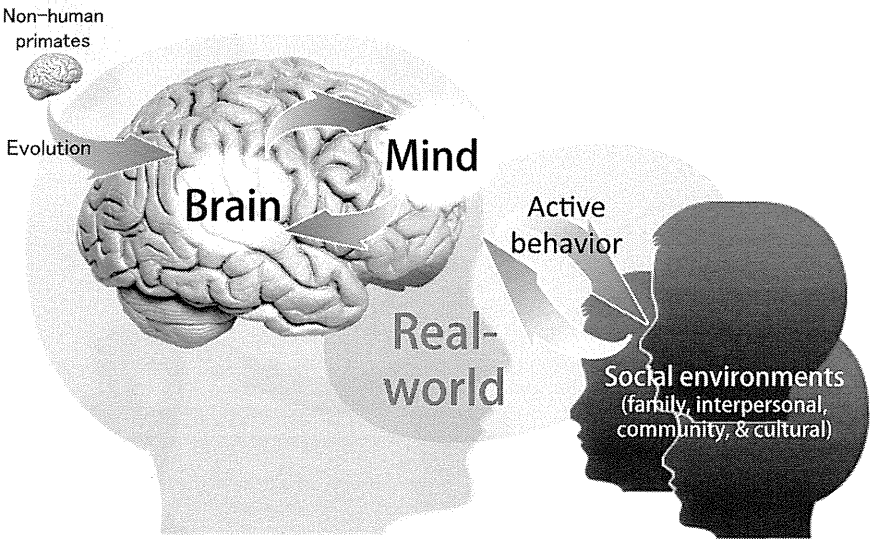

Fig. 1. The real world is where the active brain interacts with social environments.

artificial intelligence and cognitive science has been discussed as a more empirically based modeling of the human mind, language, and communication (Sun, 2000). Here we need to "ground" brain imaging onto individuals in real-world settings as action brain.

Moreover, to better understand the neural basis underlying human-specific self-regulatory behaviors that have evolved in response to selective pressure in highly complex social environments, it may be useful to adopt a comparative neuroscience approach exploring similarities and differences in characteristics between measured results from NHPs and humans.

2. "Real-world imaging" in NHPs

2.1. Historical perspectives of primate neuroscience

NHPs are social beings that acquire social adaptive behavior during development within their society (Matsuzawa, 2001). Adaptive social behavior is important for surviving as a member of the society. One of the common social behavioral features between humans and NHPs is that both are sensitive to social contexts that regulate their behavior (Adolphs, 2010). It has been reported both in NHPs and humans that larger social relations are associated with denser networks due to complex contextual processing (Kanai et al., 2012; Sallet et al., 2011). Social contexts are continuously updating our behavioral rules (Fujii and Iriki, 2012) by integrating multiple social factors (i.e., hierarchical relationship and past social history with other agents, intention of self and others, and relative spatial positions) (Byrne, 2003; Fujii et al., 2007; Iacoboni et al., 2005; Wood and Hauser, 2008) so that it continuously influences behavioral decisions. As a comparative approach and a precursor to elucidating human social brain function, understanding the neural mechanisms of adaptive behavior in primates will shed light on those in humans (Barrett et al., 2007; Capitanio and Emborg, 2008). These studies are especially useful because extensive invasive methods can be applied that are not appropriate in human subjects.

Historically, NHP social behavior has been studied in ethology field research in the wild (Goodall, 1986). For instance, the social structure and behaviors of Japanese macaques have been extensively studied (Matsuzawa, 2001). When ethologists are asked why they observe and learn animal's behavior in wild, they would laughingly respond that it is obvious because the wild environment is where their social adaptive behaviors were evolved and acquired. If animals are isolated from their natural environment, their social behavior will be completely different and less adaptive. This suggests that the natural social environment and adaptive behaviors are inseparable, and it is likely to be the same in humans.

However, previous neuroscience research has not successfully incorporated the natural social environment into experimental setups due to various technical limitations (Nagasaka et al., 2011). The natural social environment contains an infinite amount of information that cannot be controlled, and it is difficult to scientifically and quantitatively describe this information. In general, if parameters cannot be precisely monitored or controlled, scientists tend to reduce their influence by changing the study's dimensions. The most unpredictable social parameter is the behavior of another agent and was the variable to be removed from the environment of the first NHP neurophysiology studies in the 1950s. Therefore most experiments have been performed in artificial white or dark rooms totally isolated from social reality to assess single brains. The massive dimensional reductions as a result of this approach have stifled social neuroscience with regard to the elucidation of inter-agent interaction and self-regulation in social reality.

In the natural social settings, interactions with other agents significantly influence our behavioral decisions. To make socially correct decisions, we have to examine the other agent's behavior, understand their intention, and then regulate behavior to perform socially correct actions. To understand the neural mechanism of the social decision making, neuroscientists have separately investigated the neural mechanisms of face perception (Tsao et al., 2008) and action recognition (Nelissen et al., 2011; Rizzolatti and Craighero, 2004). For instance, face perception is an important function when two agents are facing each other in social reality. During facial processing, emotional states (Adolphs, 2002) and gaze direction (Senju and Johnson, 2009) are extracted and used as hints for self-regulation. However, the experiments cited above used visual stimuli displayed on computer screen; subjects were isolated from social reality because there was no dynamic or bi-directional interaction. Even though face perception studies were carried out in a socially isolated space, the results were informative. Researchers determined that facial processing requires multiple cortical foci termed "face patches" (Tsao et al., 2008) and are now searching for more detailed mechanisms. However, it remains an open question how these face patches work in real social environments.

Recognition of agent's intention was first correlated to activity in mirror neurons in the ventral premotor cortex (PMv) (Gallese

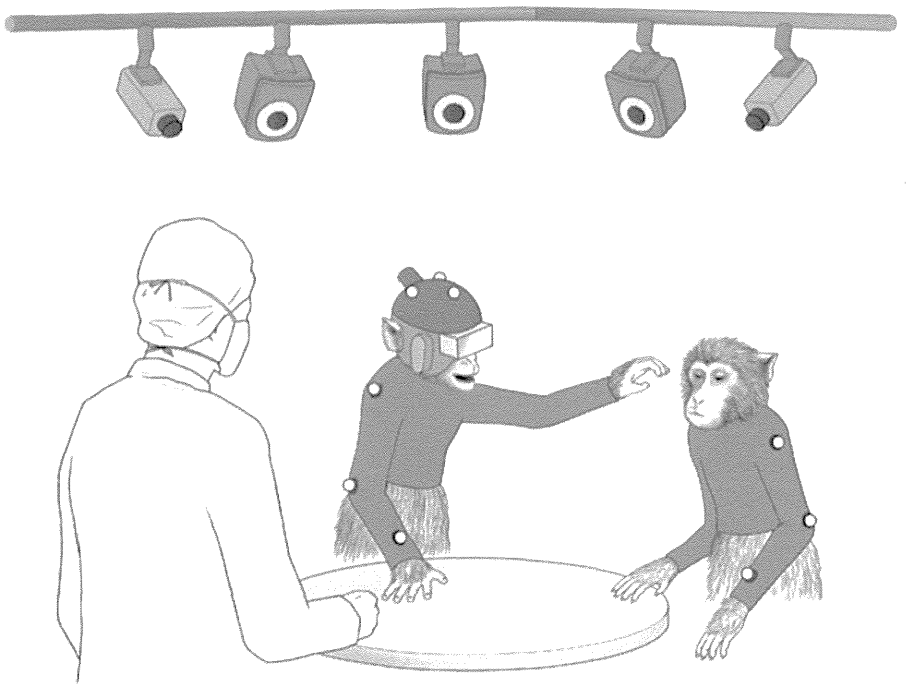

Fig. 2. Illustration of a multi-dimensional recording (MDR) environment where two monkeys are interacting with each other.

et al., 1996) and later in the parietal cortex (Fogassi et al., 2005). This is an example of the successful introduction of realistic social environments into an experimental setting. The researchers used real experimenter's actions as visual stimuli in an open social setting. Some have criticized that mirror neuron descriptions are qualitative and subjective due to the less controlled stimuli and environment that are not properly addressed yet.

Mirror neuron studies have raised two important issues in performing experiment in natural social settings. One is the importance of quantitative behavioral monitoring and the other is the importance of detailed environmental recording, because both of information are essential in post hoc analysis to see contribution of uncontrolled parameters. Since, in natural social settings, we cannot control all of environmental information, we have to record behavioral and environmental information as much as possible to address the post hoc questions.

2.2. Investigations into the active brain using real-world imaging in NHP

To overcome this criticism in experiment in natural social setting, we developed a multi-dimensional recording (MDR) technique in which all of a monkeys' behaviors are quantitatively recorded by a motion capture system, head-free eye tracking system, and conventional video camera (Nagasaka et al., 2011) (Fig. 2). Other biological data (e.g., muscle activity, heart rate, respiration rate, and skin conductance) can also be accommodated on the same MDR platform. We successfully used this technique to quantitatively describe monkeys' interactive social behavior by converting their natural behaviors into a sequence of social events to analyze neural activity. We initially recorded single-cell activity and found that parietal and prefrontal neurons modulated responses depending on social behavioral states when monkeys were socially interacting each other (Fujii et al., 2007, 2009) (Fig. 1).

We later upgraded our neural recording technique to elucidate complex network structures. Conventional neuroscience has made it possible to manipulate and record different levels of neural activity, from the molecular to neural population levels, but most studies have focused on small portions of single neurons within single brain regions. For instance, neural activity in mirror neuron studies was mostly recorded at the single-cell level but not the inter-regional level. Even when multiple regions were targeted, separate recordings were performed for each, making it impossible to observe dynamic interactions between the brain regions. The minimal requirement to reveal dynamic network structures of adaptive social behavior is to simultaneously cover different regions. The ideal situation would require high temporal resolution recordings from multiple whole brains that are interacting in a social reality. Cross-regional recording is essential because social brain function integrates multimodal information from multiple brain regions and uses the integrated social information, often termed the social context, to make adaptive social decisions. If we miss the integration and decision process achieved by cross-regional network processing, we will never be able to understand social brain function. Moreover, if we want to understand neural interactions between individuals, we have to perform simultaneous neural recordings from multiple brains.

For the sake of recording from several brain regions and multiple brains in a natural social setting, MDR employed an electrocorticogram (ECoG) array that is often used in the clinic to identify the cortical foci of epileptic seizures in human patients. ECoG can cover large cortical areas and stably record neural activity over time with a high temporal resolution (<1 kHz) (Chao et al., 2010). This allows researchers to measure directional information flow in the social brain network (Seth, 2010). Because ECoG has been used to study human cognitive functions (Hill et al., 2012) and MDR can perform simultaneous ECoG and electroencephalogram (EEG) recording, the results obtained by MDR in NHP can be a translational path toward understanding human social brain functions.

MDR allows enhancing degrees of freedom in parametric dimensions of experimental settings; however, it does not necessarily mean the experiment should be done without behavioral constraints. The advantage of MDR is that an experimenter can choose

levels of the constraints. We can start neural recordings at a conventional constraint level and gradually increase degrees of freedom in behavior depending on experimental requirements. For instance, for studying neural mechanism of eye movement, MDR allows multiple steps in behavioral control, (1) head- and body-fixed condition in the isolation box, (2) head-free but body-fixed condition in the isolation box, (3) head- and body-free condition in the isolation box and (4) head- and body-free condition in the social environment. These manipulations can be continuously done in the same animal and with the same signal quality that could never be possible in conventional methods.

MDR collects massive data that often cause difficulty in analysis. Especially there is no standard method for understanding dynamical modulation of network structure. One solution we suggest is using data mining method that will reveal hidden network structures from the massive data without subjective bias (Chao and Fujii, 2013). At the same time, the same dataset should be shared on public server to address other questions that will be raised from other researchers. In our case, all of data published on journals are shared in our data sharing service, Neurotycho.org (Nagasaka et al., 2011). The data sharing will accelerate the speed of understanding complex neural network.

It has become possible to track and analyze whole-brain activity in NHPs in natural social settings; this was only a dream in the early days of primate neurophysiology. Such studies will provide novel findings to improve our understanding of human brain functions. We would like to emphasize that the minimal requirement in understanding adaptive brain function is dynamic coupling between agents in reality.

3. Real-world neuroimaging in humans and its application in psychiatry

3.1. Significance of real-world neuroscience in human and potential neuroimaging modalities for it

Although real-world neuroscience can be attained in NHP studies by combining traditional neuronal activity recording and sophisticated behavioral recording as described in Section 2.2, real-world neuroimaging is indispensable in human studies. For example, discrepancies between neurocognitive and social cognitive abilities as laboratory findings ("capacities") and actual performance in everyday livings ("capabilities") have been gradually recognized as important research topics in psychiatric disorders; in general, psychiatric patients demonstrate fairly preserved neurocognitive and social cognitive abilities when compelled in laboratory settings but fail to exhibit them voluntarily in everyday livings. Clarification of neuroscience substrates of discrepancy between capacities and capabilities through real-world neuroimaging is expected to lead a new step toward neuroscience of ability and performance.

Neuroimaging modalities already employed in real-world neuroscience studies include fMRI and near-infrared spectroscopy (NIRS). The advantages of fMRI include high spatial resolution and established experimental designs and data analysis software, but it is limited in that subjects have to remain still during examinations in a noisy environment. NIRS is superior to fMRI in that it affords better temporal resolution and subjects can be examined in a sitting position while they speak and move; but it is also hindered by lower spatial resolution and is limited to superficial brain structures (Dieler et al., 2012; Ferrari and Quaresima, 2012). However, NIRS has been shown to be useful as a clinical auxiliary laboratory test for the differential diagnosis of depressive states (Takizawa et al., 2014).

3.2. Two-person neuroimaging as real-world neuroscience

3.2.1. Two-person neuroscience and neuroimaging

The simultaneous examination of brain function in multiple subjects was first proposed as "hyperscanning" (Montague et al., 2002). This neuroimaging concept has been widely proposed by many researchers using various terminologies: two-body neuroscience (Dumas, 2011), interactive brains (Sänger et al., 2011; Di Paolo and De Jaegher, 2012), two-brain approach (Konvalinka and Roepstorff, 2012), second-person interaction (de Bruin et al., 2012), and dark matter of social neuroscience (Pryzrembel et al., 2012). All these suggestions are pioneering in two points: (1) they try to elucidate functional relationships between two brains during mutually active interactions, instead of isolated brain processing of delivered stimuli (two-person nature), and (2) brain functions are monitored in rather natural situations as compared with conventional brain research settings (real-world nature). Both are two important points that characterize action brain as described in Section 1. Two-person neuroscience and neuroimaging will be surely useful for elucidating the brain mechanisms underlying interpersonal relationships. It will be also helpful in psychology, for example, in clarifying the brain substrates of variability of interpersonal relationship-related traits in healthy subjects. Furthermore, it is expected to advance the field of psychiatry because interpersonal relationship difficulties are one of the core pathophysiologies in many psychiatric disorders including schizophrenia, bipolar disorder, and autism spectrum disorders.

3.2.2. Published fMRI and NIRS studies

Two-person neuroimaging studies have been extensively reviewed by Konvalinka and Roepstorff (2012) and Babiloni and Astolfi (2014), who assessed nearly 30 original articles that employed fMRI, NIRS, and EEG as hyperscanning methodologies. In the original articles, the brain mechanisms of interpersonal interaction were investigated using correlational, coherence, and causality analyses that compared neuroimaging data *between* two subjects in addition to data analyses within each subject. The tasks employed to reveal interpersonal relationship in hyperscanning studies can be categorized into four groups: (1) empathy tasks that require subjects to infer the thoughts or emotions of another subject through their facial expression, gaze direction, or a cooperation game (for example, Saito et al., 2010; Kawamachi et al., 2013); (2) cooperation tasks that required subjects to jointly accomplish a given goal such as simultaneous button pressing, eye contact, movement synchronization, imitation, and a cooperation game (for example, Funane et al., 2011; Cui et al., 2012; Dommer et al., in press; Holper et al., 2012); (3) opposing multiple player tasks such as the Trust Game and the Prisoner's Dilemma game where subjects are supposed to be competitors; and (4) mutual tasks such as conversation where communication itself is the object of interpersonal behaviors and participants are supposed to be collaborators (for example, Jiang et al., 2012). Empathy, cooperation, opposing, and mutual tasks represent different aspects of interpersonal relationships and are expected to be useful in clarifying the brain substrates underlying social interactions.

3.2.3. Conversation as mutual interpersonal relationship

Conversation is one of the typical examples of the above-mentioned fourth category of interpersonal relationships that can only be examined in humans. The authors' group used NIRS to investigate brain function during real 15-s conversations. Clear activations of frontal and temporal regions in healthy subjects were demonstrated during the conversation period, and there were also smaller activations during the utterance sub-period. Larger activation in frontal regions corresponds to a lower cooperativeness personality trait as assessed with the Temperament and Character

Inventory, suggesting that subjects with less cooperative personality must make a greater effort (Suda et al., 2010). Similarly, smaller activation in the left temporal region corresponds to a higher autistic trait as assessed with the Autism-Spectrum Quotient, especially in male subjects, suggesting deficits in activation of the left temporal social brain in subjects with higher autistic traits (Suda et al., 2011). The successful observation of these relationships may be due to the real-world nature of NIRS.

Such two-person neuroimaging in real-world situations using NIRS is also promising for elucidating brain mechanisms of interpersonal dysfunction in psychiatric disorders. Participants with schizophrenia were characterized by decreased activation in the bilateral temporal lobes and right inferior frontal gyrus during the conversation task (Takei et al., 2013). The decreased activations in the left temporal lobe and right inferior frontal gyrus negatively correlated with the disorganization and negative symptoms. Subjects with major depressive disorder and bipolar disorder also demonstrated decreased activation in the left dorsolateral prefrontal and left frontopolar cortices, as well as a rapid decrease in bilateral frontopolar activation. The latter finding positively correlated with Global Assessment of Functioning scores in the major depressive disorder group (Takei et al., in press).

4. Research questions and future goals

4.1. Integration with adolescent neuroscience

Adolescence is the life stage during which individuals establish their ego through self-regulation under their social reputation from peers (Kasai, 2013). Real-world neuroimaging will be useful for understanding how adolescents self-regulate their own brain and mind in the setting of peer pressure. These types of investigations will contribute to the emerging field of adolescent neuroscience and epidemiology (Casey et al., 2010; Ormel et al., 2012).

4.2. Integration with comparative neuroscience

Recently, the concept of translatable brain marker has become increasingly important in neuroscience research. This refers to bridging the gap between human and primate brain imaging by using a measurement method commonly used in both species (e.g., MRI, ECoG, EEG, etc.) (Nagai et al., 2013). The concept of the real-world measurement should be incorporated and integrated into the endeavor of establishing translatable brain markers in neurocircuit research.

4.3. Applications in clinical psychiatry and mental health

The disability-adjusted life years (DALYs) of psychiatric disorders are an indicator of a disease's impact on life and activities, and DALYs outweigh diseases such as cancers and cardiovascular disorders (Prince et al., 2007; Wittchen et al., 2011). The high DALYs in psychiatric disorders are due partly to the high prevalence of these conditions in the general population (Kessler et al., 2005) and also because psychiatric disorder onset is common during adolescence (Kessler et al., 2005; Paus et al., 2008). As a result, the social dysfunction that generally characterizes psychiatric disorders often persists for a long period. Thus, the essential goal for psychiatric intervention is addressing social dysfunction in the daily life, and this requires an objective assessment for brain dysfunction associated with social maladaptation in real-world situations.

The integration of social epidemiology and neuroscience is becoming a powerful strategy to understand how altered social environment perception can be internalized and individualized to alter brain circuits and consequently elevate the risk of psychiatric disorder development (Akdeniz et al., 2014). Real-world imaging technologies will be useful for precisely monitoring human brain function in the context of social environmental risk factors.

4.4. Beyond the action brain: the symbolizing brain

The sixth stage of brain research will be the symbolizing brain era that emphasizes its symbolizing ability in complicated representation systems such as language and its integration of the sensing, emotional, social, ego, and action brains. Four aspects of language serve as indispensable bases of five aspects of brain function: written language as memory storage means of unlimited capacity underlies sensing brain function; spoken language as a communication tool with emotional connotations underlies social and emotional brain function; internalized language as thought and self-reflected cognition underlies ego brain function; and internalized language as self-generated guides to motivate, execute, and monitor one's own behaviors in the action brain. Through these four aspects, language plays a pivotal role in integrating all aspects of brain function.

In addition, the inter-individual nature of language development with regard to both phylogeny and ontogeny shapes the fundamental features of human mental function. It involves the parallel development of brain function as hardware and language as software, and both are critical when processing interactive information with others. This interactive nature of brain and language development underlies the inter-individual origin of mental function, which is in contrast to the reductionism hypothesis of mental function assuming intra-individual origin. The parallel nature of brain and language development results in interdependent and reciprocally influences between brain and language, in contrast to the reductionism hypothesis of mental function assuming a one-way cause–effect relation originating from the brain. These integrating views of the relationship between brain and mental functions are based on the above mentioned real-world concept and will lead to the sixth research era of the symbolizing brain.

Conflict of interest

The authors have no conflicts of interest relevant to this work.

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analgesics, hormone therapy, anticonvulsants and α-lipoic acid.[5] Considering the high incidence of psychiatric features, it seemed that the psychiatric interventions for BMS were underestimated with only few randomized control trials focusing on treating BMS with psychotropic agents.

In our opinion, BMS may include the disturbance of both the physiological and psychological systems. Anxiety, depression, pain disorder, hypochondriasis as well as delusional disorder should be considered for BMS. Thus, when clinicians see BMS patients, besides arranging a detailed physical examination, the psychological aspects should also be considered and psychiatric consultation may be needed. In this way, there will be a more comprehensive consideration for BMS.

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Psychological symptom and social functioning subscales of the modified Global Assessment of Functioning scale: Reliability and validity of the Japanese version

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THE GLOBAL ASSESSMENT of Functioning (GAF) scale and the Social and Occupational Functioning Scale (SOFAS) easily and quickly evaluate overall function using a single continuous value with anchor points, and they are widely used in both clinical and research settings.[1] These scales, however, are subject to variability and can be influenced by the rater's level of education and experience and training with the scale, as well as the quality and quantity of the patient's clinical information. Thus, the modified GAF (mGAF-original) scale was developed to improve the reliability and validity of the original GAF scale.[2] We obtained the author's permission to translate the mGAF-original scale into Japanese and to make new scales using the items and anchor points in it. Subsequently, we developed the Japanese version of the mGAF-original scale as well as the psychological symptom (mGAF-S) and social functioning (mGAF-F) subscales by splitting the items and anchor points of the mGAF-original scale. We used the lower value of the mGAF-S and mGAF-F scores for the mGAF score in accordance with instructions of the original GAF evaluation.[1] We tested inter-rater reliability and concurrent validity for the new subscales.

Developed scales, and detailed methods and results are shown in Supporting information. To test inter-rater reliability, five professionals administered the original and modified GAF scales to five patients with schizophrenia. To test concurrent validity, 10 professionals administered the original and modified GAF scales, and the Positive and Negative Syndrome Scale (PANSS) to 31 patients with schizophrenia. Participants gave written informed consent.

The intra-class correlation coefficients (ICC) of the mGAF-original, mGAF-S, mGAF-F, and mGAF scales were 0.94, 0.8, 0.96, and 0.96, respectively. The mGAF-original score was significantly correlated with the GAF score ($r = 0.91$, $P < 0.001$), and the mGAF score was significantly correlated with the GAF and mGAF-original scores (mGAF and GAF: $r = 0.89$, $P < 0.001$; mGAF and mGAF-original: $r = 0.97$, $P < 0.001$). The mGAF-S score was significantly correlated with the PANSS positive ($r = -0.54$, $P = 0.002$), negative ($r = -0.50$, $P = 0.004$), general psychopathology ($r = -0.59$, $P < 0.001$), and total scores ($r = -0.61$, $P < 0.001$). The mGAF-F score significantly correlated with the SOFAS score ($r = 0.88$, $P < 0.001$).

Our study showed excellent inter-rater reliability and concurrent validity of the Japanese versions of the mGAF-original, mGAF-S, mGAF-F, and mGAF scales. These modified versions of the GAF scale may be easier and more appropriate when separately evaluating current psychological symptoms and social functioning than the original GAF and SOFAS scales.

The Japanese version of the mGAF-original, mGAF-S, mGAF-F, and mGAF scales are available within research settings for Japanese participants, and readers can contact the corresponding author (http://npsy.umin.jp/indicator.html) if they would like to use them.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Modified Global Assessment of Functioning (GAF) scale.
Appendix S2. Detailed method.

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An fMRI study of visual lexical decision in patients with schizophrenia and clinical high-risk individuals

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ABSTRACT

Disturbances in semantic and phonological aspects of language processing are indicated in patients with schizophrenia, and in high-risk individuals for schizophrenia. To uncover neural correlates of the disturbances, a previous functional magnetic resonance imaging (fMRI) study using a visual lexical decision task in block design reported less leftward lateralization in the inferior frontal cortices, in patients with schizophrenia and individuals with high genetic risk for psychosis compared with normal control subjects. However, to our knowledge, no previous study has investigated contrasts between word and non-word processing that allow dissociation between semantic and phonological processing using event-related design visual lexical decision fMRI tasks in subjects with ultra-high-risk for psychosis (UHR) and patients with schizophrenia. In the current study, 20 patients with schizophrenia, 11 UHR, and 20 demographically matched controls underwent lexical decision fMRI tasks. Compared with controls, both schizophrenia and UHR groups showed significantly decreased activity in response to non-words compared with words in the inferior frontal regions. Additionally, decreased leftward lateralization in the non-word compared with word activity contrast was found in subjects with UHR compared with controls, which was not evident in patients with schizophrenia. The present findings suggest neural correlates of difficulty in phonological aspects of language processing during non-word processing in contrast to word, which at least partially commonly underlies the pathophysiology of schizophrenia and UHR. Together with a previous study in genetic high-risk subjects, the current results also suggest that reduced functional lateralization in the language-related frontal cortex may be a vulnerability marker for schizophrenia. Furthermore, the current result may suggest that the genetic basis of psychosis is presumed to be related to the evolution of the language capacity characteristic of humans.

1. Introduction

Disturbances in semantic and phonological processing of language have been indicated in patients with schizophrenia and in high-risk individuals for schizophrenia (DeLisi, 2001; Revheim et al., 2006; Crow, 2008; Strelnikov, 2010). Previous neuroimaging studies have reported aberrant brain activity and structural deviations related to deficits in language processing in people with schizophrenia, and in those at high-risk for psychosis (Kubicki et al., 2003; Crow, 2004; Li et al., 2009; Kubicki et al., 2011; Li et al., 2012; Thermenos et al., 2013).

To study neural correlates of semantic and phonological processing, functional magnetic resonance imaging (fMRI) tasks including lexical decision, which stands for word and non-word discrimination, with healthy volunteers have consistently shown stronger word than non-word activity associated with semantic processing occurring in a distributed left hemisphere network, and greater non-word activity associated with phonological processing occurring in the inferior frontal area (Coltheart et al., 2001; Binder et al., 2003; Ischebeck et al., 2004). Most of these studies have related greater activity to non-word than word to the conversion of graphemes into phonemes (Heim et al., 2005). Grapheme-to-phoneme conversion has been assumed to be stronger for processing non-words compared with words, because the former do not have representations of their sound form in the mental lexicon, which implies that the sound form of non-words must be reconstructed in letter-by-letter fashion during reading (Heim et al., 2005).

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Interestingly, a previous fMRI study using a visual lexical decision block design task reported more bilateral activity in the inferior frontal gyrus (IFG) in patients with schizophrenia and genetic high-risk individuals, compared with normal controls in the lexical decision task block in contrast to rest condition (Li et al., 2007a). Leftward lateralization of brain activity related to lexical decision and speech processing has been reported to be significantly reduced in patients with schizophrenia compared with healthy controls (Sommer et al., 2001, 2003; Ngan et al., 2003), and reduced interhemispheric cooperation in schizophrenia during lexical decision has been reported (Barnett et al., 2007; Mohr et al., 2008). Previous neuropsychological studies have reported relationships between phonological processing deficits and impaired reading comprehension in patients with schizophrenia (Revheim et al., 2006; Arnott et al., 2011). However, to our knowledge, no previous study discriminating between non-word and word processing using event-related design fMRI has been conducted in patients with schizophrenia. Furthermore, it is also important to investigate clinical high-risk (ultra-high-risk: UHR) individuals for psychosis (Yung et al., 2003), in which there is an opportunity to identify potential markers of a high-risk state for psychosis and schizophrenia (Pantelis et al., 2009).

To address these issues, the current study employed an event-related design lexical decision fMRI task to investigate brain activity presumed to be related to phonological processing separately from those related to semantic processing in participants with schizophrenia and those with UHR. Based on previous literature, it was expected that reductions in activity in non-word compared with word in the IFG would be found in clinical populations compared with healthy controls. Furthermore, we also hypothesized that left lateralization of brain activity in the IFG would be less evident in the clinical groups.

2. Materials and methods

2.1. Participants

Fifty-one Japanese right-handed (Oldfield, 1971) subjects participated in this study. The subject recruitment site, eligibility criteria for each diagnosis, and clinical and demographic assessment methods were the same as those used in our previous studies (Iwashiro et al., 2012; Natsubori et al., 2013) (see Supplementary Table 1). Thirty-one participants comprised the clinical groups, consisting of 20 patients with schizophrenia and 11 individuals with UHR. Briefly, the diagnoses of patients with schizophrenia were determined according to the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Axis I Disorder (SCID-I) Clinical Version (First et al., 1997a). The inclusion criteria for individuals with UHR were aged between 15 and 30 years and who had received a diagnosis of UHR according to the Structured Interview for Prodromal Symptoms (SIPS) (Miller et al., 1999; Kobayashi et al., 2007). Psychiatric symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) within 7 days before and after their magnetic resonance imaging (MRI) scan. All participants with schizophrenia and three participants with UHR received antipsychotics. Twenty healthy control subjects participated in the current study. The healthy controls were screened for neuropsychiatric disorders through the SCID-I Non-patient Edition (First et al., 1997b). Their gender, parental socioeconomic status (SES; Hollingshead, 1965), and intelligence quotient (IQ; Matsuoka and Kim, 2006; Matsuoka et al., 2006; Uetsuki et al., 2006) were not significantly different compared with the clinical groups. The control subjects were age-matched to the subjects with schizophrenia, but were significantly older compared with UHR subjects ($t(29) = 6.8$, $p < 0.001$). Thus, age was treated as a potential confounding covariate in subsequent comparisons between UHR and control subjects.

The exclusion criteria for all groups were a current or past neurological illness, a previous traumatic brain injury with any known cognitive consequences or loss of consciousness for more than 5 min, a history of electroconvulsive therapy, autism spectrum disorder that met DSM-IV criteria, and previous substance abuse or dependence based on clinical histories. Additional exclusion criteria for the controls were a history of psychiatric disease in the subjects themselves or of axis I disorders in their first-degree relatives. The ethical committee of the University of Tokyo Hospital approved this study (Nos. 1350 and 2226). After a complete explanation of the study to participants, written informed consent was obtained from every participant and from the parent if the participant was under 20 years old (Table 1).

Table 1
Clinical and demographic characteristics of study participants.

	Patients with schizophrenia (n = 20)		Patients with UHR (n = 11)		Control participants (n = 20)		*df*	F or *t* test or χ^2 values	p Value
	Mean (range)	S.D.	Mean	S.D.	Mean	S.D.			
Gender (male/female)	12/8		7/4		11/9		2	0.24	0.89
Age	29.4 (17–42)	9.0	20.5 (17–23)	2.1	28.7 (24–37)	3.7	2.48	8.3	0.001[a]
Handedness[b]	94.0	13.6	87.0	20.4	99.0	3.1	2.48	3.1	0.052
SES[c]	3.6	1.2	2.7	1.5	1.7	0.5	2.48	15.7	<0.001[d]
Parental SES	2.4	0.5	2.1	0.8	2.3	0.4	2.48	0.8	0.48
IQ[e]	105.2	10.6	107.7	10.0	108.7	8.5	2.48	0.7	0.52
PANSS score									
Total	72.2	16.7	70.8	16.3	NA		29	0.2	0.83
Positive	14.9	5.1	15.0	2.8	NA		29	−0.06	0.95
Negative	21.2	4.8	19.4	6.3	NA		29	0.9	0.37
General psychopathology	36.1	8.2	36.5	8.6	NA		29	−0.1	0.9
Onset of illness, years	23.4	5.8	NA		NA		NA	NA	NA
Duration of illness, months	74.7	70.9	NA		NA		NA	NA	NA
Antipsychotic dose[f], mg/day	874.6	673.4	29.6	53.4	NA		29	4.1	<0.001

Abbreviations: UHR, ultra-high risk for psychosis; NA, data not applicable; PANSS, positive and negative syndrome scale; SES, socioeconomic status.

[a] Post hoc independent two-tailed *t*-test indicated that controls were significantly older compared with UHR participants ($p < 0.001$), but the difference between controls and patients with schizophrenia was not significant ($p = 0.75$).

[b] Determined using the Edinburgh Inventory (Oldfield, 1971): Scores >0 indicate right-handedness. A score of 100 indicates strong right-handedness.

[c] Assessed using the Hollingshead scale (Hollingshead, 1965). Higher scores indicate lower status. Higher scores indicate lower educational and/or occupational status.

[d] Post hoc test indicated that controls were significantly different from both of the patient groups ($p < 0.01$, independent two-tailed *t*-tests).

[e] Estimated from scores on the Japanese Adult Reading Test (JART 25; Matsuoka and Kim, 2006; Matsuoka et al., 2006; Uetsuki et al., 2006).

[f] Calculated by chlorpromazine equivalents.

2.2. Behavioral procedure

A lexical decision task served as the behavioral task, using an event-related design, during fMRI scans. Participants were presented with one item after another in pseudorandom fashion from a group of stimuli consisting of 12 real words and 12 non-words (i.e., a word that could not be recognized as a real word) in total. Stimuli were shown on a screen using Presentation 2.2 software (Neurobehavioral Systems, Inc., San Francisco, CA, USA), for 500 ms with a 7–10 s stimulus onset interval of passive crosshair fixations to allow capture of the full hemodynamic response. Participants were instructed to press one of two buttons as quickly as possible to determine whether the stimulus presented was a real word or a non-word. Participants were asked to repeat these procedures twice with completely different word sets, but under the same rules. Correct rates (CR) and reaction times (RT) were recorded for each participant. For the stimuli, 48 nouns were taken from the *Lexical Properties of Japanese* (http://www.kecl.ntt.co.jp/icl/lirg/resources/goitokusei/) (Amano et al., 2008), and 24 of those were used to construct non-words by changing a syllable of existing Kana words. Word character and mora (a unit in phonology; Otake et al., 1993; Verdonschot et al., 2011) counts were matched between real words and non-words ($t(46) = -0.83$, $p = 0.41$; $t(46) = 1.19$, $p = 0.24$, respectively) (see Supplementary Table 2).

2.3. MRI scanning

A 3 T MR scanner (GE Signa HDxt, Milwaukee, WI, USA) was used in this experiment. Gradient-echo echo-planar sequences were used for functional imaging (repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 90°, slice thickness = 4.0 mm, 32 slices, field of view (FOV) = 240 mm, and matrix = 64 × 64). A total of 219 volumes were acquired over a period of 237.5 s as a session for all participants. A trained neuroradiologist (O.A., H.T., H.S., or W.G.) evaluated the anatomical MRI scans obtained through previously described methods (Natsubori et al., 2013) and found no gross abnormalities in any participant.

2.4. Behavioral analysis

All statistical analyses of behavioral data were conducted using PASW Statistics 18 (SPSS Inc., Chicago, IL, USA). For group comparisons of behavioral data related to the lexical decision task, repeated-measures analysis of covariance (ANCOVA) was conducted using CR or RT as the dependent variable, diagnosis (NC/UHR/Sc) as a between-subjects factor, condition (word/non-word) as a within-subjects factor, and age as a covariate. The significance level was set at $p < 0.05$.

2.5. fMRI analysis

The fMRI data were analyzed using SPM8 (The Wellcome Department of Imaging Neuroscience, London, UK, http://www.fil.ion.ucl.ac.uk/spm). The first 10 volumes were excluded from analysis for the equilibrium of longitudinal magnetization. Functional images were realigned, slice timing corrected, normalized to the default EPI template, smoothed (full width half maximum = 8 mm, Gaussian filtered), and high-pass temporal filtered (128 s cut-off period).

For our event-related fMRI design, in single-subject level analyses, we used a general linear model with five regressors: two types of stimuli (words/non-words) × two types of responses (correct/incorrect) and fixation. Each event-related regressor had an onset at the time of stimuli presentation and a duration that corresponded to the response time. The six motion parameters resulting from realignment (x/y/z/pitch/yaw/row) were also included as regressors to account for residual effects of head motion.

Lexicality effects were assessed by contrasting brain responses to words with those to non-words in which subjects made correct lexical decisions. Regions of interest (ROIs) were selected for differences in hemodynamic response magnitude between words and non-words based on related previous studies (Binder et al., 2003; Ischebeck et al., 2004; Li et al., 2007b). The selected ROIs for the contrast of greater responses to non-words compared with words were the bilateral IFG (Brodmann's area (BA) 44/45, 47), bilateral SMA (BA 6, 8), and bilateral middle frontal gyri (MFG; BA 46, 9). For the contrast of greater responses to words compared with non-words, selected ROIs included the bilateral temporo-parietal region (BA 39/40), left superior/middle frontal gyri (BA 6, 8, 9), bilateral anterior cingulate gyri (ACC; BA 32, 24), bilateral posterior cingulate gyri and precuneus (BA 23/31, 30, 7), and the left middle/inferior temporal gyri (BA 20/21, 37).

The group level analysis was based on a random-effects model. The thresholds for statistical significance were defined based on recent fMRI studies in patients with schizophrenia or those at high-risk with similar sample sizes (Holt et al., 2011; Choi et al., 2012; Das et al., 2012; de Achaval et al., 2012). The within-group statistical parameter maps of t values for each of the diagnostic groups were thresholded at uncorrected $p < 0.001$, and a cluster size greater than 10 voxels. For between-group analyses, two sample t-tests were performed, with age as a covariate when contrasting controls with UHR subjects. T statistic images were thresholded at uncorrected $p < 0.001$ if the peak coordinates were located in ROIs. The cluster size threshold was set at >10 voxels in uncorrected $p < 0.01$ statistical maps. And a false discovery rate (FDR) (Genovese et al., 2002) of $p < 0.05$ was adapted for peaks in other regions.

2.6. Functional ROI laterality index analysis

To further investigate diagnostic differences in neural correlates of lexical decision, laterality indices (LI) were calculated using the formula: $(L - R) / (|L| + |R|)$ (Li et al., 2007a), where L and R are the signal intensities from the contrast of non-word to word in the current lexical decision task in the left and right functional ROIs described below. The coordinates of the functional ROIs were determined at significant peak coordinates in the bilateral IFG from between-group t-statistic images of the present study (see Results), and at the exactly contralateral coordinates, with the spatial extent of a sphere with a 10-mm radius for each functional ROI. Functional ROIs in contrast to anatomical ROIs were examined to study differences in laterality from the functional perspective. For group comparisons of LI, we used an independent t-test to compare the schizophrenia group with controls, and a one-factor ANCOVA to compare UHR subjects with controls, with age as a covariate. Statistical significance was accepted at $p < 0.05$.

3. Results

3.1. Behavioral results

The CR of all participants reached above 90% for words and 60% for non-words. Repeated-measures ANCOVA showed no significant interaction or main effect of diagnosis and condition on CR or RT ($p > 0.09$) (Supplementary Table 3). These results indicate that there was no significant difference in task performance between diagnostic groups.

3.2. fMRI results

In the within-group exploratory whole brain analyses of lexicality effects (Fig. 1), a group of brain areas showed significantly greater responses to non-words compared with words in the control group. These included the bilateral IFG (BA 44/45, 47), left SMA (BA 6/8), and the right MFG (BA 9, 46). In participants with schizophrenia, the activity was similar to the control group, whereas participants with UHR had no supra-threshold activity in this contrast.

For the contrast of greater activity to words compared with non-words in the control group, a set of areas, located in the left superior frontal gyrus (BA 6), bilateral middle/posterior cingulate gyri (23, 31),

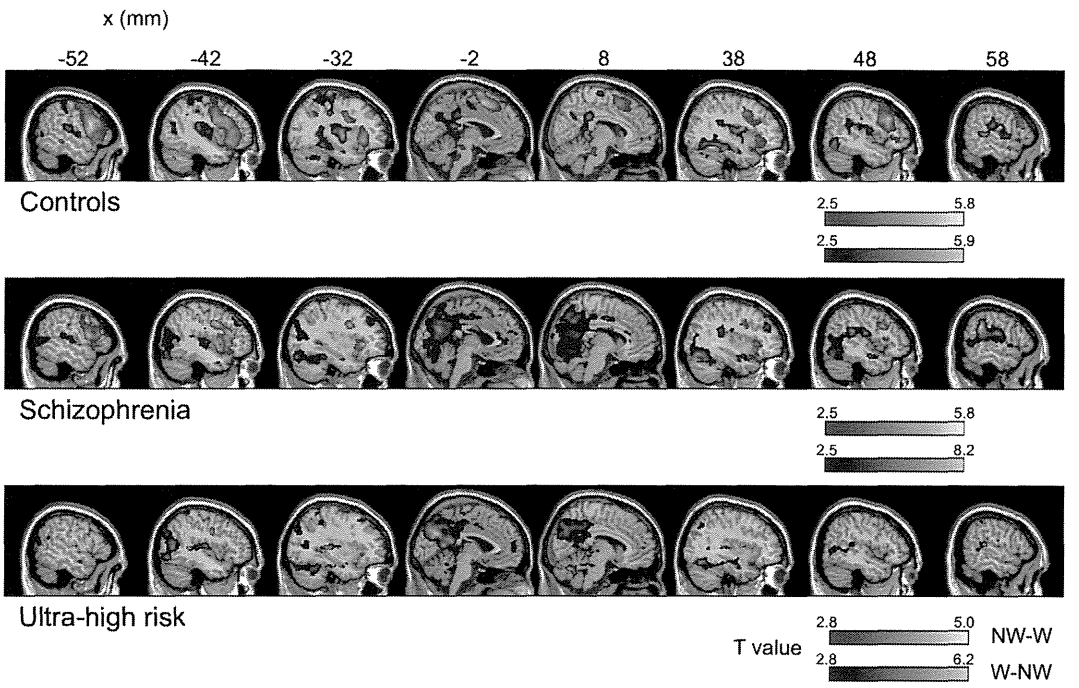

Fig. 1. fMRI results of word/non-word and non-word/word contrasts. The group average activity maps were superimposed in color on serial sagittal slices from a representative brain. The color scale refers to *t* values corresponding to uncorrected $p < 0.01$ for the purposes of presentation. Positive values are shown in red-yellow and indicate greater activity associated with non-words (NW) compared with words (W). Negative values are shown in blue-green and indicate greater activity associated with W than NW. Left–right (x) stereotaxic coordinates are given above the panels of normal controls.

left inferior temporal gyrus (BA 37), and the left supramarginal gyrus (BA 40) showed significant activity. In participants with schizophrenia or those with UHR, activities were similar to the control group, but with additional activity as shown in Supplementary Table 3.

In the between-group analyses, brain areas with greater responses to non-words compared with words were explored first. When each of the clinical groups were compared with the control group, significantly decreased activity was commonly observed in the inferior frontal regions, corresponding to BA 44/45. Additionally, significantly decreased activity in the left SMA was found in patients with schizophrenia compared with controls (Fig. 2, Table 2). When brain areas with greater activity associated with words compared with non-words were explored, no significant activity was observed compared with controls in either of the clinical groups.

3.3. Functional ROI LI analysis

Peak voxels in the contrast of greater activity to non-words compared with words in the comparison of schizophrenia with the control group ([−42, 12, 24]), and UHR and the control group ([−32, 16, 20] and [52, 24, 18]) were determined as the center of functional ROIs for the between-group analyses of LI. The LI at the coordinates (−32, 16, 20) was significantly decreased in the UHR group (mean ± SD: 0.006 ± 0.626) compared with the control group (0.253 ± 0.632) ($F(1.28) = 5.7$, $p = 0.024$). There was no significant difference in other comparisons between the LI of clinical and non-clinical groups (see Table 3 for the summary of signal intensity in functional ROIs).

4. Discussion

The current study revealed significantly decreased brain activity to non-words compared with words in the inferior frontal regions in schizophrenia and UHR participants compared with controls. Furthermore, decreased leftward lateralization related to the lexical decision task was found in the UHR group compared with the control group, and not in patients with schizophrenia. The difference in lateralization between clinical groups may indicate the differential underlying biological basis of the high-risk state and schizophrenia.

The brain regions activated in the contrast of non-words compared with words and words to non-words in the current study generally well replicated those seen in previous studies, with similar event-related design fMRI tasks in healthy subjects (Binder et al., 2003; Ischebeck et al., 2004; Heim et al., 2005). In line with these studies, Li et al. (2007) showed greater activity in the left IFG in the lexical decision task blocks compared with non-linguistic blocks in normal controls (Li et al., 2007b). The authors also showed lower-than-normal activity of IFG in the same contrast in the schizophrenia and genetic high-risk groups. Thus, brain functional abnormalities related to language processing might arise early on in the illness and may even be present prior to the onset of schizophrenia (Li et al., 2009). The current results are consistent with this notion and further add to previous studies with respect to clinical high-risk state patients and the event-related design of the fMRI task, which revealed the difference between word and non-word lexical decision.

Brain structural deficits in the inferior frontal cortices and language-processing related abnormalities have also been reported in subjects with schizophrenia and high-risk individuals. Volumetric MRI studies have reported significantly reduced volume in frontotemporal regions including bilateral IFG in subjects with schizophrenia (Onitsuka et al., 2004; Yamasue et al., 2004; Suga et al., 2009). Studies in clinical high-risk subjects have reported gray matter volume reductions in the IFG as well as lateral and medial temporal regions (Pantelis et al., 2007; Takahashi et al., 2009; Iwashiro et al., 2012). Anatomical changes in schizophrenia have been suggested to be related to asymmetries of the human brain and linked to sex (Crow et al., 1989, 2013). From the neuropsychological perspective, verbal learning and memory was reported to be one of the most sensitive measures in discriminating clinical high-risk individuals from controls (Seidman et al., 2010), and later transition to psychosis was associated with premorbid verbal fluency and memory deficits (Fusar-Poli et al., 2012). These studies indicate that language-related brain structural and neuropsychological abnormalities are present in those at high-risk, and could be a marker of