

Language-dependent performance on the letter fluency task in patients with schizophrenia

Chika Sumiyoshi^{a,*}, Aygun Ertugrul^b, A. Elif Anil Yağcıoğlu^b, Ajanta Roy^c, Karu Jayathilake^c, Alan Milby^d, Herbert Y. Meltzer^e, Tomiki Sumiyoshi^f

^a Faculty of Human Development and Culture, Fukushima University, 1 Kanayagawa, Fukushima, 960–1296 Fukushima, Japan

^b Department of Psychiatry, Hacettepe University Faculty of Medicine, 06100 Sıhhiye, Ankara Turkey

^c Department of Psychiatry, Vanderbilt University Faculty of Medicine, 2201 West End Ave., Nashville 37235, TN, USA

^d British Council, Tokyo, 1-2 Kagurazaka, Shinjuku-ku, 162–0825 Tokyo, Japan

^e Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, 446 East Ontario #7-200, Chicago, 60611, IL USA

^f National Center of Neurology and Psychiatry, 4-1-1 Ogawa-Higashi, Kodaira, 187-8551 Tokyo, Japan

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ABSTRACT

Two types of verbal fluency tasks (letter fluency task; LFT, category fluency task; CFT) have been widely used to assess cognitive function in people with psychiatric diseases including schizophrenia. The task demand of the LFT is considered to vary across languages, as the cognitive process largely relies on sound and writing systems. Specifically, a sound unit for a letter (s) and a manner of association between them are assumed to be related with the performance. In the current study, three analyses have been conducted to examine this issue, using Japanese, Turkish, and English-speaking patients with schizophrenia. It was hypothesized that severity of letter fluency impairment would be in the order of Japanese, Turkish, and English speaking patients according to the inflexibility of a word search. First, performance on the LFT and the CFT was compared among Japanese ($N = 40$), Turkish ($N = 30$), and the US ($N = 31$) patients (Analysis 1). A significant difference was found between the US and other two groups only in the LFT. Second, verbal fluency performance was compared between Japanese and Turkish patients by contrasting the degree of disassociations from normal controls (Japanese: $N = 20$, Turkish: $N = 30$) (Analysis 2). In Japanese patients, performance on the LFT was more severely impaired compared to that on the CFT while the opposite trend was found in the Turkish counterpart, suggesting that letter fluency performance was more degraded in Japanese patients. Finally, Analysis 3 was conducted to examine the relative order of letter fluency impairment among Japanese, Turkish and English-speaking patients. Disassociation in English users with schizophrenia was estimated based on previous meta-analytic reviews. The effect size (ES) for the letter fluency deficit was the largest in the Japanese sample, while the other two groups share similar ESs. The results from the three analyses partially supported the hypothesis for the severity of the letter fluency impairment in patients with schizophrenia. The language-dependency of letter fluency impairment was thought to be explained by the theoretical model built on unique properties of sound and writing systems. The considerations presented here would provide useful information for optimizing the portability of cognitive tasks across languages.

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1. Introduction

1.1. Factors affecting letter fluency performance

It is widely known that patients with schizophrenia exhibit a wide range of cognitive disturbances. The severity of impairment varies

depending on the domains of cognition. Specifically, verbal learning, executive function (e.g. planning, monitoring, inhibition), vigilance/attention, and verbal fluency have been reported to be most severely impaired (Harvey and Keefe, 1997; Reichenberg and Harvey, 2007). A particular disturbance of those domains can be assessed by several types of neurocognitive tasks. Executive function, for example, is typically assessed with Wisconsin Card Sorting Test (WCST), Stroop Test, Trail Making Test (TMT), and/or Tower of Hanoi Test. On the other hand, verbal fluency is measured with just one type of tasks: verbal fluency tasks (VFTs). VFTs are a kind of free recall tasks which consist of the letter fluency task (LFT) and the category fluency task (CFT). In the LFT, subjects are required to generate as many words beginning with a designated letter (e.g. *flower, furniture...*, for “F”) as many as possible within

Abbreviations: VFT, verbal fluency task; LFT, letter fluency task; CFT, category fluency task; BACS, the Brief Assessment of Cognition in Schizophrenia; PUG, Phonological Unit for a Grapheme; GPC, Grapheme–Phoneme Correspondence; GT Hypothesis, the Hypothesis of Granularity and Transparency.

* Corresponding author. Tel./fax: +81 24 548 8161.

E-mail address: sumiyoshi@educ.fukushima-u.ac.jp (C. Sumiyoshi).

Table 1
Characteristics of sound and writing systems in Japanese, Turkish, and English.

	Phoneme	Examples	Grapheme	Examples	Phonological unit for grapheme (PUG)	Examples	Grapheme–phoneme correspondence (GPC)	Examples
Japanese	Syllable Mora	/ka/, /ta/ /N/, /Q/	Kana	か, ㇿ	Large, coarse (Consonant + vowel)	/ka/-か, /ta/-ㇿ	Consistent, transparent (one-to-one)	か-/ka/, ㇿ-/ta/
Turkish	Consonant Vowel	/k/ /a/	Alphabet	k, a	Small, fine (Vowel, consonant)	/k/-k, /a/-a	Consistent, transparent (one-to-one)	k-/k/, a-/a/
English	Consonant Vowel	/k/, /e/ /ə/, /e/	Alphabet Dygraph	k, a th, ea	Small, fine (Vowel, consonant)	/k/-k, /ə/-a /ə/-th, /e/-ea	Loose, opaque (one-to-many, many-to-one)	a-(/ʌ/, /æ/, /ə/, ...) (k, ch...)-/k/

Note: Similar features are highlighted in double line.

a designated time (typically, 1 min). As for the CFT, a category is given as a cue for the retrieval of words (e.g. *dog, cat...* for “ANIMAL”).

VFTs are included in several neuropsychological batteries for the assessment of cognitive deficits in specific clinical conditions e.g. the Neurosensory Center Comprehensive Examination for Aphasia (Spreen and Benton, 1969), the Multilingual Aphasia Examination (Benton et al., 1994) for aphasia, the Hasegawa’s Dementia Scale Revised (Katoh et al., 1991) for dementia, the Brief Assessment of Cognition in Schizophrenia, (BACS; Keefe et al., 2004), and the MATRICS Consensus Cognitive Battery (Nuechterlein et al., 2008) for schizophrenia.

The effect of languages on evaluation for cognitive performance and functional outcome has attracted interest among researchers engaged in global clinical trials for newly developed neuroleptic agents (Harvey and Velligan, 2011; McIntosh et al., 2011; Martini et al., 2012; Velligan et al., 2012). Specifically, the feasibility of LFT has drawn attention from the developers of internationalized neuropsychological batteries, such as BACS (Keefe et al., 2004; Kaneda et al., 2007).

It has been argued that the LFT may require cognitively more intensive processing in non-alphabetical language users (Sumiyoshi et al., 2004; Suga et al., 2011; Dan et al., 2013). Despite an increasing concern for this issue, theoretical considerations for linguistic factors affecting the LFT have rarely been addressed. Although brief comments (Artiola i Fortuny et al., 1998; Harvey et al., 2002) or concise explanations were given in some studies (Sumiyoshi et al., 2004; Dan et al., 2013), more formal and systematic explanations, like the one depicted below, need to be provided.

Performance on the LFT seems to depend on sound or writing systems of relevant languages to a large degree, as subjects need to associate a given letter with sound to search a word beginning with that letter. The cognitive demand, therefore, seems to vary according to the availability of the target sound. To be linguistically precise, the notions of letters (characters) and sound discussed here are termed graphemes and phonemes, respectively. Two factors, a phonological unit for a grapheme (PUG) and grapheme–phoneme correspondence (GPC), appear to be related with the availability.

The PUG represents a minimum unit of phoneme(s) for a corresponding grapheme, i.e. the amount of phonemes a single letter (or multiple letters such as a dygraph) covers (see Table 1 for examples). In the Japanese language, for example, the PUG is typically a syllabic unit consisting of a vowel (V) or a consonant (C) plus a vowel (C + V = CV).¹ In English, on the other hand, generally a single C or

V is covered by a letter or digraph (double letters, e.g. “th” for “ea” for /e/) (Table 1). Cognitive demands for word search are considered to vary according to the size of PUG; if a PUG is relatively small, particular combinations like syllables or consonant clusters tend to be formed. In English, for instance, consonant “f” co-occurs with either a vowel (e.g. *family, find, furniture...*) or particular consonants, such as “l” (e.g. *fly, flower, fluent...*) or “r” (e.g. *friend, fragile, frame...*) (Fig. 1, the top right). Such concurrency of phonemes, like syllabic associations or consonant clusters, can be used as effective clues for searching words beginning with a designated letter. In fact, previous studies have reported that English users exploited this linguistic property on executing the LFT, producing phonologically associated words (Troyer et al., 1997; Robert et al., 1998). Probably, this factor is prominent in languages with rich syllabic structures such as English, in which syllables are formed by chunks of consonants around a vowel (e.g. CCV, CVC, and VCC).

Meanwhile, if a PUG is relatively large, such specific associations are not likely to occur. For example, in Japanese, a syllable does not have specific phonemic partners to appear with (Fig. 1, the top left). In such a circumstance, cognitive demands for word search would become greater, as subjects cannot retrieve words by relying on the concurrency of phonemes. Instead, they just have to enumerate any possible combinations of syllables to find a lexical word.

The consistency in grapheme–phoneme correspondence (GPC) is assumed to be another potential factor affecting letter fluency performance. The GPC considerably varies across writing systems (Table 1). It is rather loose in some alphabetical languages, such as English and Danish, allowing a single grapheme to associate with multiple phonemes. In contrast, other alphabetical languages, such as Spanish, Italian, Turkish, and Serbo-Croatian languages demonstrate fairly consistent GPC with nearly one-to-one grapheme–phoneme correspondence (Oney and Goldman, 1984). Likewise, in the Japanese *kana* system, the association of grapheme (a *kana*) to phoneme(s) (V or CV) is highly consistent, exhibiting almost one-to-one mapping.

Naturally, availability of the target sound in a word search becomes more stringent as the GPC approaches to perfect consistency (one-to-one). That is, finding a word with a specific initial letter would become more difficult if the number of sound alternatives is limited. For example, every Japanese *kana* is exclusively tied with one syllable (or mora), and therefore, it is not possible to search for a word beginning with a specified *kana* by recalling several syllable alternatives (Fig. 1, the bottom left). On the other hand, if a grapheme has more than one phoneme partners, as in alphabetic languages with loose GPC (e.g. English), a subject could search words among several phoneme alternatives, allowing much easier word retrievals. For instance, “a” in English corresponds to /æ/, /ɔ:/, and /ə/ sounds, which provides several candidates beginning with the letter “a” (Fig. 1, the bottom right).

¹ Technically speaking, the PUG in Japanese corresponds to a mora, suprasegmental unit based on duration of sound. Generally, V or CV forms a mora. However, some phonemes (e.g. nasal or geminate sound) exist as morae without syllabic structure but with a full beat like a syllable.

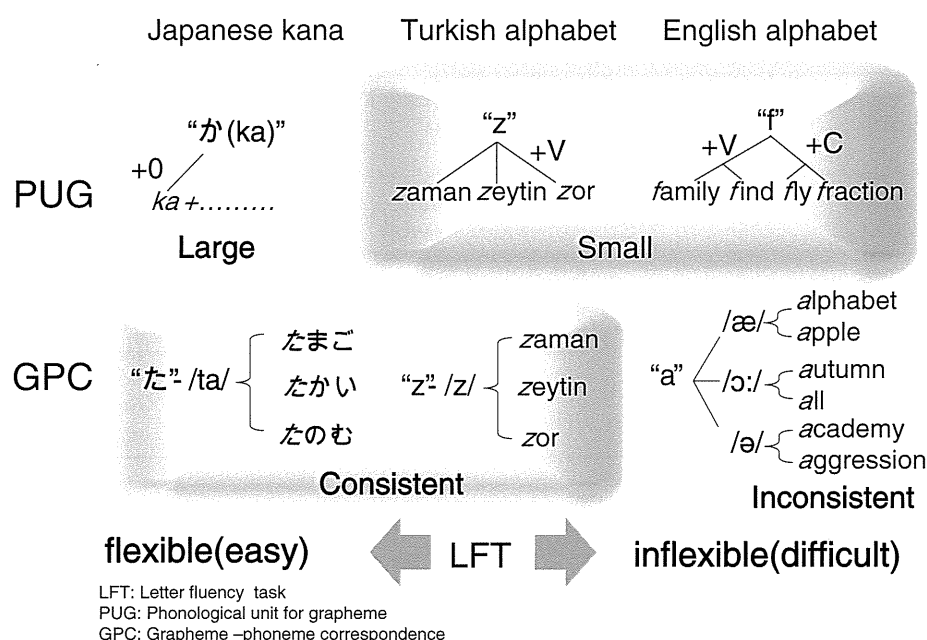


Fig. 1. Schematic representation for PUG (top) and GPC (bottom).

In summary, performance on the LFT would be more demanding in languages with a larger PUG and more consistent GPC like Japanese, due to the limited strategies to find lexical words beginning with a specified letter. Concerning other alphabetic languages such as Turkish, the cognitive demand for word search is assumed to be somewhere between Japanese and English; the PUG in Turkish is as small as English, and has certain association patterns (e.g. syllabic association of C + V), which provide a cue for searching a word (Fig. 1, the top middle). On the other hand, the GPC of Turkish is highly consistent like Japanese *kana*, with a nearly one-to-one association between graphemes and phonemes (Fig. 1, the bottom middle). In fact, it has been reported that Turkish children can decompose pseudo-words faster and more accurately than American children, as Turkish GPC is more consistent than that of English (Oney and Goldman, 1984). The similarities of the three languages regarding those linguistic factors are highlighted with double lines in Table 1.

1.2. The aim of the study

The purpose of the current study was to investigate the effect of the writing systems on letter fluency performance in patients with schizophrenia. It was hypothesized that the characteristics of writing systems, i.e. the PUG and GPC of respective languages determined the performance. Specifically, the LFT would be more severely impaired if the PUG is larger (a grapheme covers multiple phonemes), and if the GPC is more consistent (a particular grapheme corresponds exclusively to a single phonological unit).

To test this hypothesis, we compared the letter fluency performance among Japanese, Turkish, and the US (English-speaking) patients with schizophrenia. As previously noted, the writing systems of these languages uniquely vary in terms of the PUG and GPC; in Japanese, the PUG is large (single kana represents V or a CV) and the GPC is almost one-to-one (consistent). By contrast, the former is small (an alphabet or a digraph representing C or V) and the latter is one-to-many (inconsistent) in English. As for Turkish, the PUG is small (an alphabet) while the GPC is highly consistent (Table 1).

The current study consists of three analyses. First, letter fluency performance was compared among Japanese, Turkish, and the US patients with schizophrenia to examine whether the degree of impairment was in the order of Japanese > Turkish > the US patients (Analysis 1; Fig. 2, the top). Next, the difference between Japanese and Turkish patients was further explored by contrasting the degree of disassociation from normal controls to confirm selective impairment of the LFT only in Japanese patients (Analysis 2; Fig. 2, the bottom left). Thirdly, the severity of the letter fluency impairment in the three language users was evaluated based on the results from Analysis 2 and data from meta-analytic reviews for verbal fluency in English-speaking patients with schizophrenia (Analysis 3; Fig. 2, the bottom part).

Finally, the current findings were discussed in relation to the "Hypothesis of Granularity and Transparency" (Wydell and Butterworth, 1999), which was originally proposed to explain the prevalence of developmental dyslexia in countries using different languages.

2. Analysis 1: a comparison of letter fluency performance among Japanese, Turkish, and the US patients

2.1. Subjects

Forty Japanese patients, 30 Turkish patients, and 31 the US patients with schizophrenia entered the study. Demographic and clinical profiles are summarized in Table 2 (the left 3 columns). They were recruited from the University of Toyama Hospital, the Outpatient Clinic of Hacettepe University Department of Psychiatry, and the Psychiatric Hospital at Vanderbilt, respectively. The study protocol was approved by Ethics Committees of the three universities. Written informed consent was obtained from all subjects. All patients met DSM-IV or DSM-IV-TR criteria for schizophrenia (American Psychiatric Association, 1994, 2000). Diagnosis was made by experienced psychiatrists using structured interview, medical history, and all available information. Patients known to be abusing alcohol or other illicit drugs, or those with epilepsy, brain damage, or neurologic disorders, were excluded from the study.

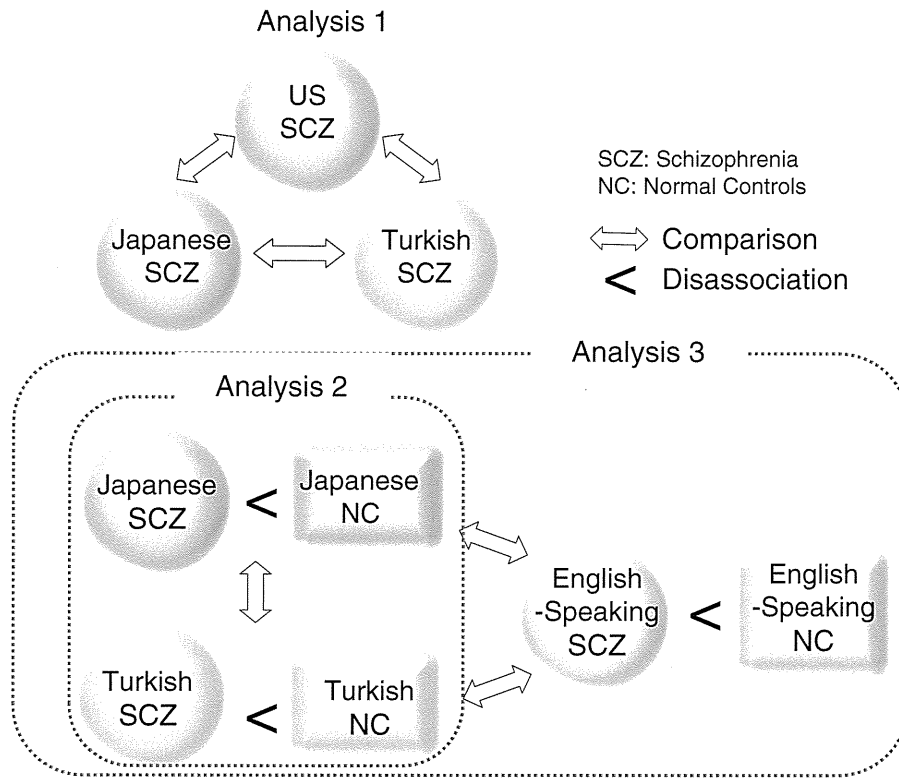


Fig. 2. Study design.

2.2. Procedure

In order to clarify the differences in performance on the LFT, data from the CFT was also included as a referencing variable. The two tasks were conducted following the standard norm (Spreen and Strauss, 1998); subjects were asked to orally produce as many words as possible in 1 min. “ANIMAL” was used as the cued category in the CFT. For the LFT, “か” (KA), and “た” (TA) were used for Japanese subjects, “A”, “E”, and “Z” for Turkish patients, and “F”, “A”, and “S” for the US subjects. The FAS version is conventional form in the US. Letters “A”, “E”, and “Z” in the Turkish version were chosen depending on a normative study done in Turkish

population (Bingöl et al., 1994). Letters in the Japanese version were chosen based on the Japanese lexical database Amano and Kondo, 2000 the occurrence of KA in general publication (16,200) was approximately twice as many as that of TA (9281) and this frequency contrast is analogous to that between “S” and “F” in the FAS version of letter fluency (Sumiyoshi et al., 2001, 2004).

2.3. Statistical analyses

Multivariate analysis of variance (MANOVA) was conducted to examine group differences in demographic and clinical variables.

Table 2 Demographic variables and verbal fluency scores.

	Analysis 1			Analysis 2	
	Japanese SCZ (N = 40)	Turkish SCZ (N = 30)	US SCZ (N = 31)	Japanese NC (N = 20)	Turkish NC (N = 30)
Age (yr)	31.58 (10.44) ^a	27.80 (6.21)	40.42 (11.04)	26.55 (9.91)	27.83 (5.99)
Male/female	24/14	18/12	26/5	16/4	18/12
Education (yr)	12.99 (2.74)	13.07 (2.29)	12.13 (1.84)	14.8 (1.91)	13.1 (2.21)
Neuroleptics dose (mg) ^b	23.14 (31.24)	0.00	6.61 (9.74)	-	-
Onset (yr)	23.94 (6.67)	22.17 (4.49)	23.30 (9.36)	-	-
Duration (yr)	7.18 (7.20)	5.37 (5.03)	12.27 (11.08)	-	-
LFT	KA: 9.66 (3.48) TA: 7.03 (3.36)	A: 9.23 (4.87) E: 7.81 (3.81) Z: 6.80 (2.70)	F: 10.83 (4.75) A: 8.47 (3.50) S: 11.50 (3.84)	14.95 (3.72) 11.65 (2.97)	12.70 (4.86) 11.17 (4.02) 9.40 (3.81)
LFT mean ^c	8.37 (3.09)	8.27 (3.35)	10.22 (3.53)	13.30 (2.97)	11.09 (3.96)
CFT ANIMAL	15.45 (4.42)	15.77 (3.79)	15.59 (4.07)	19.30 (4.53)	21.27 (4.49)

Note: LFT, letter fluency task. CFT, category fluency task. NC, normal controls. SCZ, schizophrenia.

^a Mean (standard deviation).

^b Haloperidol equivalent.

^c Averages of KA, and TA (Japanese), A, E, and Z (Turkish), and F, A, and S (US). Those mean scores were used in statistical analyses.

Group is a between-subject factor, while Age, Education, Duration of illness, and Neuroleptics are dependent variables. For verbal fluency data, one-way analysis of covariance (ANCOVA) was conducted to compare group differences of the CFT and the LFT, respectively. Age, Education, Duration of illness, and Neuroleptics were covaried.

The number of verbal outputs for ANIMAL naming was used for the CFT score. As for the LFT, the mean scores were calculated by averaging outputs for each letter used in respective language (i.e. “KA” and “TA” in Japanese, “A”, “E”, “Z” in Turkish, and “F”, “A”, “S” in the US).

The effect sizes (ESs) using Cohen's *d* and 95% confidential intervals (CIs) were calculated for comparisons between the US and Japanese, the US and Turkish, and Japanese and Turkish patients with schizophrenia.

2.4. Results

2.4.1. Demographic and clinical profiles

Means and SDs of demographic and clinical variables are shown in Table 2. MANOVA revealed an overall difference among the three groups (Wilks' lambda = 8.58, $F = 1.58$, $df = 8, 146$, $p < 0.01$). Subsequent analysis yielded significant main effects for Age ($F = 15.28$, $df = 2, 76$, $p < 0.01$), Duration of illness ($F = 20.84$, $df = 2, 76$, $p < 0.01$), and Neuroleptics ($F = 7.22$, $df = 2, 76$, $p < 0.01$), but not for Education ($F = 1.30$, $df = 2, 76$, n.s.). Multiple comparisons with Bonferroni correction demonstrated that Age and Duration of illness for the US patients were significantly higher than those for Japanese and Turkish patients ($p < 0.05$). As for Neuroleptics, a significant difference was found only between Japanese and Turkish patients (Japanese > Turkish, $p < 0.05$).

2.4.2. Verbal fluency performance

Means and SDs of data from the VFTs are shown in Table 2. As the results from ANCOVA, the group difference was obtained in the LFT ($F = 3.88$, $df = 2, 72$, $p < 0.05$), but not in the CFT ($F = 0.72$, $df = 2, 72$, $p = 0.49$). Multiple comparisons for the main effect of LFT revealed that the LFT mean score for the US patients was significantly higher than those for Japanese patients and Turkish patients ($p < 0.05$).

ESs and CIs in the comparisons of the three groups are summarized in Table 3 (the column of Analysis 1). ES between the US and Japanese and that between the US and Turkish were much larger (0.56 and 0.57, respectively) than that between Japanese and Turkish (−0.03). Moreover, CIs for the US–Japanese (0.08–1.04) and that for the US–Turkish (0.06–1.08) did not cover 0, suggesting that substantial differences existed between the US subjects and other two groups.

Table 3
ESs obtained in Analysis 1, Analysis 2, and Analysis 3.

	Analysis 1			Analysis 2		Analysis 3			Summary ES ^c
	ES ^a			ES		N			
	US–Japanese SCZ–SCZ	US–Turkish SCZ–SCZ	Turkish–Japanese SCZ–SCZ	Japanese NC–SCZ	Turkish NC–SCZ	Previous ^b studies	NC	SCZ	English-speakers NC–SCZ
LFT	0.56 (0.08, 1.04) ^a	0.57 (0.06, 1.08)	−0.03 (−0.05, −0.02)	1.53 (0.93, 2.14)	0.89 (0.36, 1.49)	9	430	586	0.83 (0.69, 0.97)
CFT	0.04 (−0.07, 0.15)	0.03 (−0.47, 0.54)	0.08 (−0.55, 0.40)	0.93 (0.36, 1.49)	1.26 (0.70, 1.81)	10	463	613	1.06 (0.93, 1.19)

Note: LFT, letter fluency task. CFT, category fluency task. NC, normal controls. SCZ, schizophrenia.

^a Cohen's *d* (95% confidential interval).

^b Studies listed in Table A.1 in Appendix.

^c Summary ES (95% confidential interval) estimated from previous studies.

2.5. Discussion

The results suggest that the letter fluency performance was more severely impaired in Japanese and Turkish patients than that in the US patients. It should be noted that the group differences were obtained after possible confounds (Age, Education, Duration of illness, and Antipsychotic dose) were controlled. Also, it is worth noting that the differences were found only in the LFT, and the CFT performances were almost equal among the three groups.

If a larger PUG affects letter fluency performance, Japanese patients would have shown severer impairment than the Turkish counterparts. The clear difference, however, was not observed in the current analysis. This issue was pursued in Analysis 2.

3. Analysis 2: a comparison for disassociations of verbal fluency in Japanese and Turkish samples

Analysis 2 was conducted to further investigate the difference in the letter fluency performance between Japanese and Turkish patients with schizophrenia. For this purpose, we focused on the degree of disassociation from normal controls in the LFT and CFT (Fig. 2, the bottom left). If cognitive demand for letter fluency is heavier in Japanese users than Turkish users, a larger disassociation in the LFT, compared to the CFT, would be expected exclusively in the Japanese patients with schizophrenia.

3.1. Subjects

Japanese and Turkish patients were the same as those used in Analysis 1. In addition, 30 Turkish and 20 Japanese normal controls participated in this analysis as reference groups (Table 2, the right 2 columns). They were mostly recruited from the university or hospital staff to be matched with the patient groups as to age and education. Written informed consent was obtained from all participants.

3.2. Procedure

The tasks and procedure were the same as those in Analysis 1.

3.3. Statistical analyses

Two-way ANCOVA was conducted for each sample separately, with Diagnosis (patients vs. normal controls) as between-subject factor, and Task (LFT vs. CFT) as within-subject factor. Age and Education were controlled as covariates. ESs and 95% CIs between normal controls and patients were estimated for the LFT and CFT, respectively.

3.4. Results

The results for verbal fluency performance for patients and normal controls are summarized in Table 2 (the middle column). Diagnosis \times Task interaction effects were significant both in Japanese and Turkish samples (Japanese: $F = 4.10$, $df = 1, 55$, $p < 0.05$, Turkish: $F = 6.30$, $df = 1, 56$, $p < 0.05$). Subsequent analyses of simple main effects revealed the contrasting trend between the two groups; as for the Japanese sample, the diagnosis effect was more distinct in the LFT ($F = 21.25$, $df = 1, 114$, $p < 0.01$) compared to the CFT ($F = 12.49$, $df = 1, 114$, $p < 0.01$). In contrast, the disassociation from normal controls was larger in the CFT ($F = 29.56$, $df = 1, 116$, $p < 0.01$) compared to the LFT ($F = 7.79$, $df = 1, 116$, $p < 0.01$) in the Turkish sample. Accordingly, the ES was larger for the LFT in the Japanese sample (LFT = 1.53 > CFT = 0.93), while the direction was reversed in the Turkish sample (LFT = 0.89 < CFT = 1.26) (Table 3).

4. Analysis 3: A comparison for disassociations of verbal fluency in Japanese, Turkish, and English-speaking samples

The results from Analysis 2 support the assumption that Japanese patients with schizophrenia exhibited greater impairment in the LFT compared to the CFT. In contrast, degradation was larger in the CFT than that in the LFT in Turkish sample. A similar trend has been observed for English users with schizophrenia (Goldberg et al., 1998; Phillips et al., 2004); letter fluency was relatively spared compared to category fluency in those samples. Thus, we sought to determine the order of intactness of letter fluency performance among the three groups of patients (Fig. 2, the bottom part). According to the easiness of execution, the robustness of the letter fluency was assumed to follow the order of English- > Turkish- > Japanese-speaking subjects with schizophrenia.

4.1. Method

As normal controls at the US site were not available in the current study, we took a meta-analytic approach to examine the disassociation in English-speaking samples; the ESs of verbal fluency in previous studies were summarized and compared with those of Japanese and Turkish samples studied here.

To our knowledge, two meta-analytic reviews of verbal fluency in schizophrenia have been reported (Bokat and Goldberg, 2003; Henrey and Crawford, 2005). Both reviews have presented different degrees of impairment between the LFT and the CFT. Based on ES analyses of 11 studies, Bokat and Goldberg (2003) reported that the LFT was relatively intact compared to the CFT in patients with schizophrenia. This finding was replicated in a more large-scaled study by Henrey and Crawford (2005), which also confirmed the robustness of performance on the LFT in patients with schizophrenia.

Although these previous reviews provide insights into the nature of verbal fluency deficits in schizophrenia, they included studies using a wide range of letters and categories. The inclusion criteria, therefore, needed to be more restrictive to contrast them with the ESs of the current study. Thus, we re-selected only the studies using “F”, “A”, and “S” (cues for the LFT) and “ANIMAL” (cues for the CFT) in the two meta-analytic reviews. Accordingly, 9 and 11 studies were chosen for the LFT and the CFT, respectively (Appendix, Table A.1). The summary ESs and 95% CIs were calculated for the selected studies, using the method by Petitti (2000); ESs were weighted by sample size of respective studies and averaged. In addition, Q statistics (Petitti, 2000) were estimated to examine the homogeneity of the results across the studies.

4.2. Results

Table 3 demonstrates the ESs between normal controls and patients of the current study (the column of Analysis 2) and the summary ESs of previous studies (the column of Analysis 3). As was reported in the original studies (Bokat and Goldberg, 2003; Henrey and Crawford, 2005), the ES for the LFT (0.83) is smaller than that for the CFT (1.06) in the English-speaking sample. Furthermore, the summary ES for the LFT is the smallest in English samples (0.83) among the three language groups (Japanese = 1.53, Turkish = 0.89).

The Q statistics were significant for the CFT ($Q = 20.29$, $df = 10$, $p < 0.05$) but not for the LFT ($Q = 10.98$, $df = 8$, *n.s.*). The result suggests that previous studies have yielded relatively uniform ESs regarding the LFT, and therefore, the summary ES for the selected 9 studies is considered to be highly reliable.

4.3. Discussion

Results from Analysis 2 and Analysis 3 confirmed that only Japanese patients elicited a relatively severe impairment on the LFT compared to CFT. Meanwhile, in contradiction to our assumption, the degree of letter fluency impairment in Turkish patients was not so severe compared to that in English-speaking patients, with ESs of 0.89 and 0.83, respectively.

5. General discussion

5.1. Summary of the study

The present study provided the evidence for the language-dependency of letter fluency performance in schizophrenia. First, verbal fluency was directly compared among Japanese, Turkish, and the US patients. Performance on the LFT was significantly worse for Japanese and Turkish patients compared to the US counterparts (Analysis 1). Second, whether the letter fluency deficit was greater for Japanese patients relative to Turkish patients was determined by comparing the disassociation from normal controls (Analysis 2). Japanese patients exhibited a larger disassociation from normal controls in the LFT compared to the CFT, while the opposite trend was found in Turkish patients, suggesting that letter fluency is more severely disturbed in Japanese patients. Finally, the degree of degradation found in Analysis 2 was contrasted to that of English-speaking patients reported in the previous literature (Analysis 3). As a result, the ES for letter fluency was the largest in Japanese patients, supporting the assumption that the LFT impairment in these patients is the greatest among the three language users. However, a clear difference in ES was not found between Turkish patients and English-speaking counterpart.

5.2. Modified GT hypothesis for the letter fluency performance

As noted before, cognitive demands for execution of the LFT is assumed to increase if the PUG (the size of the phonological unit for a grapheme) is relatively large and if the GPC (grapheme–phoneme correspondence) is highly consistent. In terms of acquiring literacy, i.e. learning to read and write in childhood, the larger PUG and highly consistent GPC may be advantageous. This concept is represented by the Hypothesis of Granularity Transparency model (the GT hypothesis; Wydell and Butterworth, 1999). “Granularity” corresponds to the size of PUG. In this theoretical framework, the PUG is called “coarse” if a single character covers a relatively larger sound unit such as a syllable (a consonant(s) plus a vowel) or a whole word (a complex of phonemes or syllables). Contrarily, it will be “fine” if a character corresponds to a single phoneme (a consonant or a vowel). “Transparency” refers to the consistency of the GPC, which will increase as the letter-to-sound association approaches to one-to-one. On the other hand, if a letter has several alternative sounds, transparency will become “opaque”,

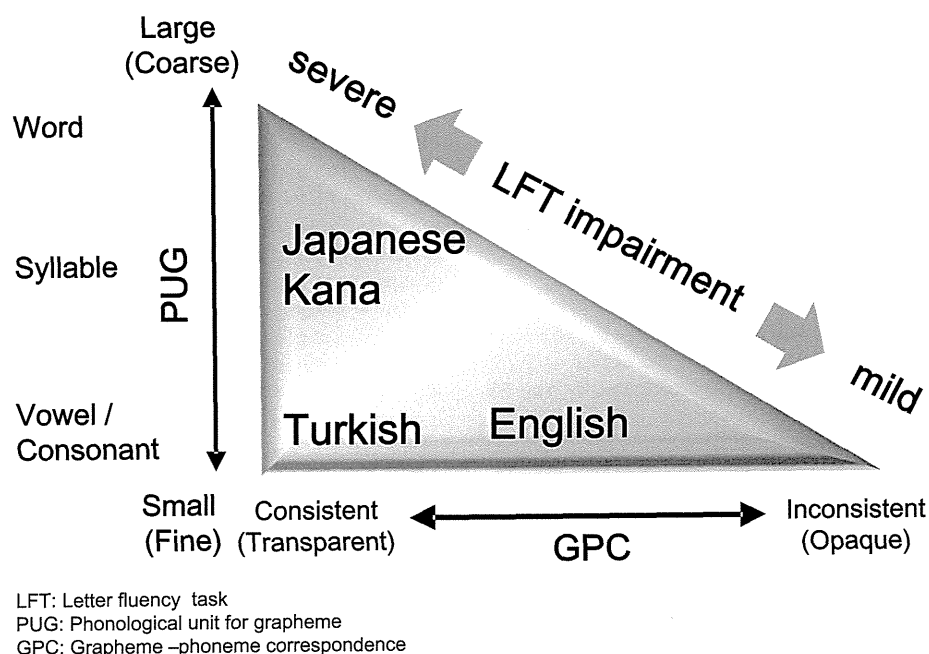


Fig. 3. Modified version of the hypothesis of granularity and transparency.

suggesting that the rules of association cannot be easily perceived (The notions are appeared in Table 1 and Fig. 3).

According to the GT hypothesis, writing systems with a coarse PUG and a transparent GPC, such as Japanese *kana*, are most easily learned. In fact, the GT hypothesis was developed to explain a unique case of developmental dyslexia (Wydell and Butterworth, 1999); a Japanese-English bilingual boy showed a dyslexic episode exclusively in English, even though his dominant spoken language was English (Wydell and Butterworth, 1999). This model was also used to explain the prevalence of developmental dyslexia which varies considerably across countries using different languages. Its incidence is approximately 7–8% in England, 3–4% in Italy (Lindgren et al., 1985; Goswami, 2000), and 0.98–1.7% in Japan (Makita, 1968; Miyazaki et al., 1995).

As the model is built on the two orthographic factors (i.e. PUG and GPC), the modified version of the GT hypothesis seems to be applied to the language-dependent impairment of letter fluency in schizophrenia. Contrary to the case with developmental dyslexia, the letter fluency deficit of schizophrenia will become severer if the PUG is coarser (larger) (Fig. 3, the vertical axis upward) and if the GPC retains higher transparency (consistency) (Fig. 3, the horizontal axis leftward) due to inflexibility in a word search. In the modified GT hypothesis, Japanese is located in the “inflexible area”, while English is placed in the “flexible area” (Fig. 3). Turkish would fall somewhere between Japanese and English, with a flexible (small) PUG and an inflexible (consistent) GPC.

The results in the current study partially support the modified GT hypothesis. First, Japanese patients and Turkish patients tended to perform worse on the LFT compared to their US counterparts (Analysis 1). Second, the larger disassociation from normal controls, in terms of letter fluency, was shown exclusively for Japanese patients (Analysis 2 and Analysis 3). On the other hand, the extensive analysis of ESs did not show a greater degree of disassociation of letter fluency in Turkish patients compared to English-speaking patients (Analysis 3). The reason for the lack of noticeable difference should be an issue of future studies.

Another limitation concerning the modified GT hypothesis is that, currently, it is theory-driven rather than evidence-based. To date, information on letter fluency in non-English speaking patients with schizophrenia (especially, in Asian countries) is scarce (Sumiyoshi et al., 2001, 2004). Large-scale cross-language surveys are required to validate

the application of the modified GT hypothesis to language-dependent disturbance of letter fluency in schizophrenia.

6. Conclusions

The current study examined language-dependent impairment in letter fluency in patients with schizophrenia based on theoretical consideration for linguistic factors affecting the performance. Two factors, i.e. the size of phonological unit for a grapheme and consistency of the grapheme-phoneme correspondence, were assumed to explain the different degree of impairment across languages, as they determine the flexibility of word search. The theoretical model based on those factors may provide an account for the language-dependent pattern of the letter fluency deficit in schizophrenia.

The effort to conceptualize the language-diversity in cognitive tasks, as we have done with the application of the modified GT hypothesis to letter fluency in patients with schizophrenia, would be beneficial for international standardization of cognitive assessment in schizophrenia.

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Contributors

CS designed study, analyzed data, and wrote the draft. TS planned and supervised the study, and organized the international collaborative team for this study. AE, EY, AR, HYM and KJ collected data and supported statistical analysis. AE, AM, and TS revised the manuscript. All authors have approved the final manuscript.

Conflict of interest

All authors declare they have no conflict of interest.

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Appendix A

Table A.1

Studies included in Analysis 3.

Study	Measure	Normal controls			Schizophrenia			Es ^a	Weighted ES 95%	CI-upper 95%	CI-lower 95%	Note
		N	Mean	SD	N	Mean	SD					
LFT												
Feinstein et al. (1998)	FAS-sum	11	44.1	12.0	23	36.3	10.2	0.70	5.60	5.74	5.47	
Gourovitch et al. (1996)	FAS-sum	27	45.3	12.4	24	34.4	10.3	0.93	10.69	10.83	10.56	
Kremen et al. (2003)	FAS-mean	83	13.5	3.5	83	10.1	4.2	0.87	33.12	33.25	32.98	
Kuperberg et al. (1998)	FAS-mean	10	18.0	5.0	27	13.0	3.0	1.33	10.09	10.22	9.95	
Moore et al. (2006)	FAS-sum	92	38.8	11.6	163	29.5	11.9	0.79	46.58	46.72	46.44	
Phillips et al. (2004)	FAS-sum	33	32.2	9.5	33	28.1	9.9	0.42	6.72	6.86	6.58	
Riley et al. (2000)	FAS-sum	40	46.0	10.3	22	30.1	11.0	1.48	18.01	18.14	17.87	
Rossell and David (2006)	FAS-sum	48	59.0	19.5	62	47.0	16.7	0.66	17.25	17.39	17.11	
Rossell et al. (1999)	FAS-sum	31	47.7	13.1	69	35.6	14.9	0.84	19.24	19.38	19.11	Calculated by averaging data from deluded and non-deluded subjects
CFT												
Aloia et al. (1996)	Animal	32	20.3	4.9	28	12.3	2.2	2.03	20.09	20.21	19.96	
Fossati et al. (1999)	Animal	14	35.2	8.8	14	23.6	5.7	1.51	8.22	8.35	8.09	2 min. version was conducted
Gourovitch et al. (1996)	Animal	24	19.8	4.3	27	12.7	4.4	1.60	15.47	15.60	15.34	
Kremen et al. (2003)	Animal	83	18.9	4.8	83	14.0	4.8	1.01	37.31	37.44	37.18	
Moelter et al. (2001)	Animal	47	28.9	7.1	38	19.3	6.6	1.38	23.67	23.80	23.54	
Moore et al. (2006)	Animal	92	18.9	4.4	163	14.7	5.1	0.86	50.07	50.20	49.94	
Paulsen et al. (1996)	Animal	28	20.5	3.4	56	15.8	4.9	1.04	19.27	19.40	19.14	
Phillips et al. (2004)	Animal	33	18.6	4.4	33	13.3	4.5	1.17	16.51	16.64	16.38	
Prescott et al. (2006)	Animal	28	23.1	7.2	40	17.6	5.4	0.88	13.67	13.80	13.54	
Rossell and David (2006)	Animal	48	21.2	5.4	62	17.2	4.9	0.77	19.79	19.92	19.66	
Rossell et al. (1999)	Animal	31	23.4	7.1	69	17.1	5.9	0.99	22.06	22.19	21.93	Calculated by averaging data from deluded and non-deluded subjects

Note: LFT, letter fluency task; CFT, category fluency task; FAS-sum—sum of scores of F, A, and S; FAS-mean—mean of scores of F, A, and S.

^a Cohen's d.

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Near-infrared spectroscopy in schizophrenia: a possible biomarker for predicting clinical outcome and treatment response

Shinsuke Koike^{1,2*}, Yukika Nishimura², Ryu Takizawa^{2,3}, Noriaki Yahata⁴ and Kiyoto Kasai²

¹ Office for Mental Health Support, Division for Counseling and Support, The University of Tokyo, Tokyo, Japan

² Department of Neuropsychiatry, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

³ Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London, UK

⁴ Department of Youth Mental Health, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Edited by:

Stefan Borgwardt, University of Basel, Switzerland

Reviewed by:

Takahiro A. Kato, Kyushu University, Japan

Masato Fukuda, Gunma University, Japan

*Correspondence:

Shinsuke Koike, Office for Mental Health Support, Division for Counseling and Support, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
e-mail: skoike-ty@umin.ac.jp

Functional near-infrared spectroscopy (fNIRS) is a relatively new technique that can measure hemoglobin changes in brain tissues, and its use in psychiatry has been progressing rapidly. Although it has several disadvantages (e.g., relatively low spatial resolution and the possibility of shallow coverage in the depth of brain regions) compared with other functional neuroimaging techniques (e.g., functional magnetic resonance imaging and positron emission tomography), fNIRS may be a candidate instrument for clinical use in psychiatry, as it can measure brain activity in naturalistic position easily and non-invasively. fNIRS instruments are also small and work silently, and can be moved almost everywhere including schools and care units. Previous fNIRS studies have shown that patients with schizophrenia have impaired activity and characteristic waveform patterns in the prefrontal cortex during the letter version of the verbal fluency task, and part of these results have been approved as one of the Advanced Medical Technologies as an aid for the differential diagnosis of depressive symptoms by the Ministry of Health, Labor and Welfare of Japan in 2009, which was the first such approval in the field of psychiatry. Moreover, previous studies suggest that the activity in the frontopolar prefrontal cortex is associated with their functions in chronic schizophrenia and is its next candidate biomarker. Future studies aimed at exploring fNIRS differences in various clinical stages, longitudinal changes, drug effects, and variations during different task paradigms will be needed to develop more accurate biomarkers that can be used to aid differential diagnosis, the comprehension of the present condition, the prediction of outcome, and the decision regarding treatment options in schizophrenia. Future fNIRS researches will require standardized measurement procedures, probe settings, analytical methods and tools, manuscript description, and database systems in an fNIRS community.

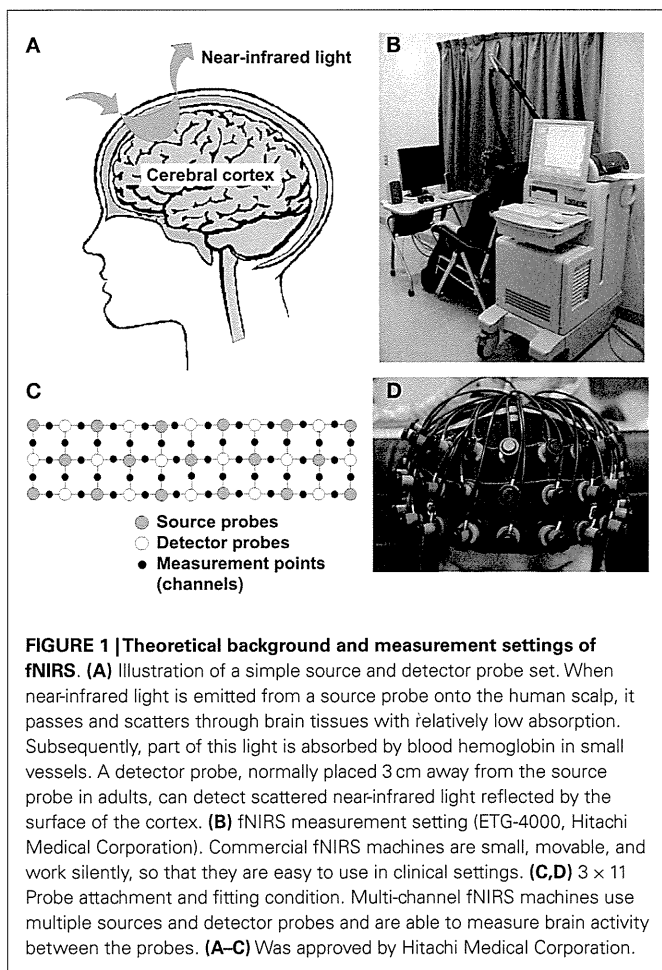
Keywords: near-infrared spectroscopy, verbal fluency task, biological markers, early intervention, clinical outcome

INTRODUCTION

Techniques that allow the easier and less invasive measurement of brain structure and activity, such as magnetic resonance imaging (MRI), functional MRI, and positron emission tomography (PET), have progressed rapidly over the past 20 years. There has been considerable expectation regarding the clinical application of neuroimaging techniques to psychological conditions and psychiatric illnesses (1, 2). Biological markers measured using neuroimaging instruments would clarify the pathophysiological features of psychiatric disorders, inform patients and family members regarding their actual conditions, and improve general impression of psychiatric disorders, by more easily giving the explanation of their conditions and discussing their assumed prognoses.

Functional near-infrared spectroscopy (fNIRS) is a functional brain imaging tool that can measure hemoglobin changes over the surface of the brain easily and non-invasively (Figure 1) (3–5). fNIRS technique was found in 1977 (6), and has been applied to

measure brain hemodynamic activity through the scalp (7, 8). The release of commercial fNIRS machines that are small, movable, and work silently during the last decade (Figure 1B) has allowed the progress of fNIRS research in the field of psychiatry (9). In 2012, more than 100 studies were published on this subject; among these, about 20 articles pertained to the field of psychiatry (9). Part of the results of those fNIRS studies has been approved as one of the Advanced Medical Technologies as an aid for the differential diagnosis of depressive symptoms by the Ministry of Health, Labor and Welfare of Japan in 2009 (10–12), as the presence of different characteristic waveform patterns in the prefrontal cortex (PFC) during a verbal fluency task (VFT) has been reported among patients with major depressive illness (4, 12–17), bipolar disorder (12, 13), and schizophrenia (4, 5, 12). This was the first such approval in the field of psychiatry in Japan (see the “Application to supplementary diagnostic tool for psychiatric disorders” subsection). Here, we reviewed fNIRS research that focused on schizophrenia, which



is currently the most published topic in the application of fNIRS in the field of psychiatry, and address future investigations that are needed for the clinical application of this technique as an aid for the differential diagnosis, comprehension of present conditions, prediction of outcome, and decision regarding treatment options in schizophrenia.

PRINCIPLES OF BRAIN ACTIVITY MEASUREMENT USING NEAR-INFRARED LIGHT

THEORETICAL BACKGROUND OF THE MEASUREMENT OF BRAIN ACTIVITY USING fNIRS INSTRUMENTS

Near-infrared light, especially that with a wavelength of 650–1000 nm, has characteristics that include a relatively high absorption through hemoglobin, as well as a relatively high penetration through bone and skin, compared with light with other wavelengths. The emission of near-infrared light from a source probe on the human scalp leads to its passing and scattering through brain tissues with relatively low absorption, followed by the absorption of part of this light by blood hemoglobin in small vessels (<1 mm) (18). A detector probe, which is normally placed 3 cm away from the source probe in adults, can detect scattered near-infrared light that is reflected by the surface of the cortex (Figure 1A). Therefore, the region located between the source and the detector probes is

generally set as a measurement area that is often called a “channel” (Figure 1C). fNIRS instruments can measure oxygenated hemoglobin (O₂Hb) and deoxygenated hemoglobin (HHb), as well as total hemoglobin (tHb) by summing up O₂Hb and HHb, by using near-infrared light with two or more different wavelengths that are slightly different from the absorption rates of O₂Hb and HHb. In accordance with light manipulation, fNIRS instruments are roughly divided into three types: continuous wave (CW), frequency domain (FD), and time domain (TD) instruments. Although CW-type fNIRS machines are unable to measure absolute hemoglobin concentration in tissues, they are relatively small, have low installation and maintenance costs, and are able to perform measurements at a high sampling rate compared with FD- and TD-type fNIRS machines (18). Therefore, recent clinical studies have used CW-type fNIRS machines (19, 20). The theoretical details of all types of fNIRS instruments were reviewed elsewhere (18, 20, 21).

ADVANTAGES AND DISADVANTAGES OF fNIRS COMPARED WITH OTHER FUNCTIONAL IMAGING INSTRUMENTS

The advantages and disadvantages of CW-type fNIRS compared with other functional imaging instruments (fMRI, PET, and EEG) are shown in Table 1. fNIRS has the following advantages: (1) non-invasiveness, which allows repetitive measurements, even in infants (21, 22); (2) easy setting; (3) small size and portability; (4) high temporal resolution compared with fMRI and PET (18, 20); (5) possibility of performing measurements in a non-restrained position, such that participants can sit on a chair, talk, and move their hands; and (6) possibility of relatively easily combining measurements with other neuroimaging techniques, such as EEG (23, 24), MRI (25–30), PET (31–33), and magnetoencephalography (MEG) (34, 35). Conversely, fNIRS has the following disadvantages: (1) low spatial resolution (10–30 mm); (2) possibility of performing measurements only at the surface of the cortex; (3) inability to measure absolute hemoglobin value (CW-type); and (4) the data obtained can be influenced by scalp, muscle, skull, and cerebrospinal fluid factors in addition to hemodynamic changes in the cortex (20).

Other than task-related hemoglobin changes derived from neural activities under neurovascular coupling, fNIRS signals vary depending on task-related blood pressure changes and skin blood flow, as well as spontaneous brain activity related to heart rate, respiration, and physiological oscillations (20, 21). Simultaneous measurements by fNIRS and pulse Doppler sonography or by fNIRS with different probe distances [e.g., shallow (5 mm) and deep (30 mm)] allow the distinction of fNIRS signals from the cortex from those of other brain tissues. A study based on fNIRS with different probe distances and laser Doppler velocimetry showed that hemoglobin changes from the cortex during the VFT may contain only 6% of fNIRS data in the PFC, and that most signal changes may arise from changes in skin blood flow (36). The results OPF simultaneous fNIRS, fMRI, MR angiography, and peripheral physiological measurements suggested that task-evoked sympathetic arterial vasoconstriction affected fNIRS signal changes substantially (37). However, a subsequent study in which simultaneous measurements using multiple fNIRS probe

Table 1 | Comparison of CW-type fNIRS machines with other neuroimaging tools.

		fNIRS	fMRI	PET	EEG	MEG
Theoretical background	Signal property	Scattered near-infrared light	Magnetic property	Uptake of ligand marked positron	Collection of neural activity	Magnetic fields produced by brain's electrical activity
	Measurement area	Surface of the cortex	Whole brain region	Whole brain region	Surface of the cortex unless using depth EEG	Surface of the cortex
	Time resolution (s)	1	2–3	≥10	0.01	0.01
	Spatial resolution (mm)	20	5	10	20	10
	Effect of extra-cortical tissue	Some	Little	Little	Some	None
Measurement setting	Invasiveness	No	No	Intravenous injection of radioactive ligand	No	No
	Body movement	Tolerable	No	No	No	No
	Head restraint	No	Yes	Yes	No	Yes
Instrument	Size	Small, movable	Large, fix	Large, fix	Large in research use	Large, fix
	Transportability	Yes	No	No	Limited	No
	Initial cost	300,000–400,000 USD^a	Several million USD	Several million USD	100,000–300,000 USD	Several million USD
	Measurement and maintenance cost	Reasonable	Moderate	Very expensive (positron ligand)	Reasonable	Moderate

Bold shows advantages compared to other neuroimaging tools.

^aETG-4000 (Hitachi Medical Corporation).

distances and laser Doppler flowmetry were performed suggested that about 50% of fNIRS signals contributed to the fNIRS signal component in the deep layer, mostly measured in the cortex, during several cognitive tasks, including the VFT (38). A study of simultaneous measurement using fMRI, fNIRS, and laser Doppler flowmeter showed that the prefrontal fNIRS signals were significantly correlated with the blood oxygenation level-dependent (BOLD) signals in the gray matter rather than those in the soft tissue or the laser Doppler signals (39). Previous studies have suggested that the ratio of fNIRS signal changes in the cortex varies from 6 to 60%, and the variation has been considered as being caused by differences in measuring instruments, estimation methods, and brain areas measured (20, 36–38, 40–44). Several studies have provided filtering methods that allow raising the ratio of task-related hemoglobin changes in the cortex to in the extra-cortical tissues; however, these systems require additional probes and complex analytical methodologies because of different near-infrared absorption and scattering coefficients in each tissue and anatomic characteristics throughout the light path in each brain area (25, 38, 40, 41). Therefore, fNIRS is a reliable tool for research based on the group-level and/or channel-cluster-level investigations, although its reliability at the individual and single-channel levels is not sufficient (18, 45–48). Few studies in clinical psychiatry have considered these filtering methods because of the limitations of measurement time and setting. Future studies will be needed to improve the signal-to-noise ratio for application over wide measurement areas without losing the advantage of fNIRS instruments.

COMPARISON OF fNIRS HEMOGLOBIN CHANGES WITH BOLD SIGNALS IN fMRI

The measurement of brain activity using the fMRI technique has progressed during the last two decades. The BOLD signal is thought to represent the differences in the magnetic properties of deoxygenated hemoglobin concentration under T2-weighted measurement conditions when cerebral blood flow (CBF) increases and HHb decreases in small vessels (49). The theoretical model of BOLD compared with fNIRS signals was reviewed in detail elsewhere (18). Briefly, localized O₂Hb decreases and HHb increases occur (i.e., initial dip) when neurons are activated in a specific region. Several seconds later, the blood flow system is triggered to request glucose to the region (i.e., hemodynamic response), which is followed by a CBF increase and peripheral vascular bed dilation, leading to tHb increase and HHb decrease in small vessels, and O₂Hb increase in blood capillaries and vascular bed. As this neurovascular coupling that occurs in the activated area is thought to vary according to brain area and vessel diameter, and to be sensitive to persistent neural activity, the relationship between hemoglobin changes and BOLD/fNIRS signals has a complex variation pattern.

Other than the difference in spatio-temporal measurement characteristics between BOLD and fNIRS signals, the BOLD signal is thought to detect mainly changes in the magnetic properties of small vessels, whereas the fNIRS signal is thought to detect changes in near-infrared light absorption in blood capillaries (50). Therefore, several discrepancies may occur between BOLD and fNIRS signals. Previous fNIRS studies have yielded inconsistent

results compared with other imaging tools. Simultaneous fNIRS and fMRI studies have shown that the BOLD signal in a specific region was associated with the O₂Hb of fNIRS signal changes in the corresponding region (25, 29, 39, 51) or with HHb changes (26–28, 30, 51). One of the explanations for these inconsistent correlation results is that most fNIRS studies have been conducted using block-designed tasks, whereas fMRI studies have mainly used an event-related design. In addition, the analysis of fMRI data by software such as Statistical Parametric Mapping (SPM) uses a hypothesis that fits a probable activation model, whereas most fNIRS studies have analyzed average signal intensity during the whole task period without any probable activation model. Differences in acquired signal handling may result in discrepancies regarding regions with significant brain activity. As O₂Hb data generally exhibit larger changes compared with HHb during cognitive activity, most clinical fNIRS studies have mainly been analyzed using O₂Hb data.

ESTIMATION OF BRAIN AREA

As more studies have focused on the spatial characteristics of brain activity using multi-channel fNIRS instruments, the need to clarify the estimated location of each probe in the cortex and each channel on the scalp has arisen. As reviewed by Tsuzuki et al. recently (52), several methodologies can estimate brain areas at each probe and channel, such as structural MRI measurement using fNIRS probe marks for each participant (53, 54), a probabilistic registration method using a 3D digitizer (55), and a probabilistic virtual registration method without any additional instrument (56). As the virtual registration method enables the estimation of brain areas based on standard brain images at each probe and channel by defining only probe setting based on the 10–20 system electrode locations, and because this method has similar accuracy compared with other estimation methodologies (56), most fNIRS studies have applied this method to estimate the measurement brain areas of channels. fNIRS software can also use the virtual registration method as a toolbox (<http://www.jichi.ac.jp/brainlab/tools.html>) (57). There are several standard stereotaxic coordinate systems such as the Montreal Neurological Institute (MNI) and the Talairach Daemon. The LONI Probabilistic Brain Atlas (LPBA40) (58) system has been often used in fNIRS studies based on probabilistic registration methods (3, 52, 59, 60).

APPLICATION OF fNIRS IN SCHIZOPHRENIA RESEARCH

Schizophrenia is a syndrome that is characterized by positive and negative symptoms and cognitive dysfunction with enduring social deficits. Moreover, it affects approximately 0.7% of the general population (2). The World Health Organization reported that the estimated burden of schizophrenia accounts for 2.3% of all diseases worldwide, and its disability-adjusted life year ranks ninth among all non-communicable diseases (61). However, effective treatments and objective indices for all symptoms and functions of schizophrenia have not been fully met.

Since the first fNIRS report of altered activation patterns in schizophrenia compared with healthy controls was published in 1994 (62), fNIRS research focusing on schizophrenia has been the most published topic in the field of psychiatry (9). We reviewed

systematically research articles published up to April 1, 2013, by searching PubMed and Web of Science. As in previous systematic reviews (9, 18), we used “[(near infrared) OR (optical topography)] AND (schizo* OR psycho*) AND (brain OR cortex)” as a search term. Two hundred and sixty articles were extracted, among which 29 explored brain activity in patients with schizophrenia. Half of these articles (15 articles, including 4 studies of genetic variants) adopted a VFT as an activation cognitive battery during measurement.

VERBAL FLUENCY TASK

The VFT is a popular cognitive task that is used in neuropsychological tests and neuroimaging measurements to explore various cognitive functions during verbal recall, retrieval, working memory, attention, and inhibition (avoiding inappropriate words) (63, 64). During the task, participants are instructed to say as many words from a given paradigm as possible in a given time (usually 60 s). This paradigm is roughly divided into semantic (category fluency task, CFT), such as fruits, or phonological (letter fluency task, LFT), such as words that begin with the letter “p.” Neuropsychological studies have revealed that patients with schizophrenia have worse VFT performances compared with healthy controls (65). Although fMRI and fNIRS studies have shown that relatively global brain activity occurs during the VFT compared with a task that requires specific cognitive domains, such as the n-back working-memory task (28, 66) and the go/no-go task (67), most participants (including patients with chronic schizophrenia) can perform the task (10, 11, 19, 63, 64).

Eleven previous VFT studies are listed in **Table 2**. Watanabe and Kato firstly described that patients with schizophrenia had reduced O₂Hb and HHb changes in the left PFC during the LFT compared with healthy controls (68). This study also demonstrated that patients who were medicated with atypical antipsychotics had better task performances and similar O₂Hb changes compared with controls, suggesting that typical antipsychotics may impair task response and brain activity. However, that study did not explore whether impaired O₂Hb changes were derived from impaired task response or functional impairment in the PFC, which may be ameliorated by atypical antipsychotics. Suto et al. firstly described the spatio-temporal activity patterns in the PFC and temporal cortex among patients with depression and schizophrenia and healthy controls using two 24-channel fNIRS machines (4). In that study, a modified task procedure was adopted in which three initial syllables changed in turn every 20 s during a 60 s task period, to help participants avoid silence and reduce differences in task performances among groups. Patients with schizophrenia had lower activity in the bilateral PFC and temporal cortex at the start of the task period compared with controls, whereas patients with depression had lower activity in the bilateral PFC and temporal cortex across the task period. These results were irrespective of task performance, and the task paradigm used in that study was used widely in further studies. In addition, this result was based on the Advanced Medical Technologies in Japan (10–12). Using a larger cohort, Takizawa et al. replicated the observation that patients with schizophrenia had slower and inappropriate activity after the task period compared with healthy controls (5). Furthermore, activities in the frontopolar prefrontal cortex (FPC) region were positively

Table 2 | Previous fNIRS studies in schizophrenia using verbal fluency tasks.

Reference	Place	fNIRS instrument		Case demographics			
		Model ^a	Number of analyzed channels	Number of cases (M/F)	Mean age in cases (SD)	Medication	Recruitment places
Shimodera et al. (73)	Kochi	OMM-3000/16	42	32 (12/19)	42.4 (15.7)	All	University hospital
Koike et al. (3)	Tokyo	ETG-4000	52	38 (22/16) ^b	31.3 (6.1) ^b	All ^b	University hospital, psychiatric hospital, health service center, and clinics
Takeshi et al. (72)	Tokyo (Toho University)	OMM-3000/16	24	18 (7/11)	25.4 (5.8)	All	NA
Azechi et al. (70)	Osaka	OMM-3000/16	2	30 (16/14) ^c	39.6 (13.1) ^c	All	University hospital
Quaresima et al. (69)	L'Aquila	NIRO-300	2	9 (5/4)	32.1 (8.3)	All	NA
Ikezawa et al. (71)	Osaka	NIRO-200	2	30 (12/18)	38.7 (11.7)	Two patients drug naïve ^d	University hospital
Takizawa et al. (5)	Tokyo	ETG-4000	52	55 (26/29)	40.1 (11.1)	All	University hospital
Ehlis et al. (74)	Wuerzburg	ETG-100	22	12 (9/3)	34.2 (10.4)	One patient drug naïve	NA
Kubota et al. (75)	Cleveland	NIRO-300	2	16 (8/8)	37.5 (13.0)	All	NA
Suto et al. (4)	Gunma	ETG-100	48	13 (9/4)	37.9 (12.0)	All	University hospital
Watanabe and Kato (68)	Ehime	HEO-200	1	62 (30/32)	40.1 (12.3)	All	Psychiatric hospital

Reference	Task setting			Results ^e		
	Pre-task condition	Task condition	Post-task condition	Patients compared to controls	Estimated regions for group differences	Multiple analysis correlation
Shimodera et al. (73)	30-s Rest	30-s × 2 Letter sets	70-s Rest	↓	Bilateral FPC, DLPFC, and VLPFC regions	Bonferroni
Koike et al. (3)	60-s Vowel repeats	20-s × 3 Letter sets	70-s Vowel repeats	↓ ^f	Bilateral FPC, DLPFC, and VLPFC regions ^f	FDR
Takeshi et al. (72)	60-s Vowel repeats	20-s × 3 Letter sets	70-s Vowel repeats	↓	Bilateral dorsal FPC and DLPFC	No
Azechi et al. (70)	30-s Vowel repeats	20-s × 3 Letter/category sets	60-s Vowel repeats	↓ ^g	Bilateral FPC	No
Quaresima et al. (69)	120-s Rest	30-s × 4 Letter sets	No setting	↓	Bilateral FPC	No
Ikezawa et al. (71)	30-s Vowel repeats	20-s × 3 Letter/category sets	60-s Vowel repeats	↓ ^g	Bilateral FPC	ANCOVA
Takizawa et al. (5)	60-s Vowel repeats	20-s × 3 Letter sets	70-s Vowel repeats	↓	Bilateral FPC, DLPFC, and VLPFC regions	FDR
Ehlis et al. (74)	10-s Rest	30-s Letter/category and 30-s rest × 2 sets	30-s Control task (repeatedly say weekdays) and 30-s rest between the sets of task conditions	↓ ^g	Left DLPFC and VLPFC	ANOVA

(Continued)

Table 2 | Continued

Reference	Task setting			Results ^e		
	Pre-task condition	Task condition	Post-task condition	Patients compared to controls	Estimated regions for group differences	Multiple analysis correlation
Kubota et al. (75)	20-s A vowel repeats	15-s × 6 Letter/category sets	No setting	↓ ^g	Bilateral FPC	ANOVA
Suto et al. (4)	30-s Vowel repeats	20-s × 3 Letter sets	60-s Vowel repeats	–	–	ANOVA
Watanabe and Kato (68)	15-s No detailed description	60-s One letter set	15-s No detailed description	↓	Left FPC	ANOVA

Reference	Correlational analysis between clinical variables and fNIRS signals		
	GAF	Other clinical variables	Medication
Shimodera et al. (73)	NA	n.s.	NA
Koike et al. (3)	Positive association in the FPC region in the chronic schizophrenia group	Positive association with PANSS positive or negative scores in the FEP group	n.s. (including no difference between UHR individuals with and without medication)
Takeshi et al. (72)	n.s., But positive association in the FPC during an idea fluency task	NA	NA
Azechi et al. (70)	NA	n.s.	n.s.
Quaresima et al. (69)	NA	NA	NA
Ikezawa et al. (71)	NA	n.s.	n.s.
Takizawa et al. (5)	Positive association in the FPC and right DLPFC regions	Negative correlation with age at measurement, positive correlation with PANSS positive score, and negative correlation with PANSS general psychopathology score in schizophrenia	n.s.
Ehlis et al. (74)	NA	NA	n.s.
Kubota et al. (75)	NA	NA	NA
Suto et al. (4)	NA	NA	NA
Watanabe and Kato (68)	NA	n.s.	n.s.

Excluded previous gene association studies.

NA, not applicable; n.s., no significant correlation; FPC, the frontopolar prefrontal cortex; DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; FDR, false discovery rate; GAF, the global assessment of functioning; PANSS, the positive and negative symptom scale; FEP, first-episode psychosis, UHR, ultra-high risk.

^aOMM-3000/16, Shimadzu Corporation; ETG-4000 and ETG-100, Hitachi Medical Corporation; NIRO-300 and NIRO-200, Hamamatsu Photonics Corporation; HEO-200, Omron Healthcare Corporation.

^bExhibit case in the chronic schizophrenia group. Sixteen UHR and 2 FEP individuals were antipsychotics naïve and 8 UHR and 1 FEP individuals were drug naïve.

^cAs Azechi et al. (70) used the same sample from Ikezawa et al. (71) as the First group, we describe for the Second group.

^dBy Azechi et al. (70).

^eResults from brain activity during the whole of the task period.

^fResults in the chronic schizophrenia group.

^gResults during the letter fluency tasks.

associated with global assessment of functioning scores in schizophrenia. Quaresima et al. replicated the finding of reduced brain activity in schizophrenia during the LFT, whereas no significant

change was observed during a visual spatial working memory task (69). Ikezawa et al. and Azechi et al. showed the efficacy of the LFT task in fNIRS (70, 71). Ikezawa et al. measured hemoglobin

changes in the PFC using a two-channel fNIRS instrument during the LFT, CFT, Tower of Hanoi (TOH), the Sternberg task, and the Stroop task, and showed that brain activities during the LFT and TOH were significantly different between patients with schizophrenia and healthy controls (71). Azechi et al. explored this further using discrimination analysis and showed that 88.3% of participants correctly discriminated between patients and controls based on task performance on the TOH, LFT, and CFT, and on fNIRS signals during the VFT (70). This result confirmed that 75% of independent participants were able to discriminate correctly using the same procedure. Koike et al. explored the signal differences among different clinical stages of schizophrenia (ultra-high risk, first-episode psychosis, and chronic schizophrenia) and showed that the activities in the FPC, ventrolateral PFC (VLPFC), and temporal cortex were lower in patients than they were in controls, whereas the activities in the dorsolateral PFC (DLPFC) decreased with advancing clinical stage (3). Those authors also replicated the finding that the activity in the FPC region was positively associated with global assessment of functioning scores in chronic schizophrenia, implying that it may be a candidate biomarker for the assessment of psychological condition in schizophrenia (3, 5). Takeshi et al. measured brain activity during the idea fluency task, which is thought to require more executive function, and showed that patients with schizophrenia had decreased activity in the ventral area of the PFC (72). Furthermore, these signal changes were positively associated with the global assessment of functioning scores, whereas O₂Hb changes during the LFT were not. Shimodera et al. replicated the characteristic waveforms in schizophrenia, such as smaller initial activity at the start of the task period, reduced activity during the task period, and inappropriate activity after the task period, and used a numerical calculation (73).

The CFT has also been used in fNIRS studies, which often compare this task to the LFT. Kubota et al. used a two-channel fNIRS instrument to show for the first time that healthy controls had larger activity in the PFC during the LFT than in the CFT under similar task performances, whereas patients with schizophrenia had smaller activity during the LFT than during the CFT (75). Patients with schizophrenia had smaller activity than did healthy controls under similar task performances between the groups. This result is consistent with those of other studies (70, 71). Ehlis et al. used a multi-channel fNIRS instrument that covered the left frontotemporal region and found that healthy controls had larger and spatially wider activities during the LFT compared with the CFT (74), which was then replicated by measuring wider areas of the bilateral prefrontal/temporal cortices (76). Ehlis et al. also replicated the finding that patients with schizophrenia had significantly reduced activities compared with healthy controls during LFT, but not during the CFT.

APPLICATION OF fNIRS AS A SUPPLEMENTARY DIAGNOSIS TOOL FOR PSYCHIATRIC DISORDERS

As described above, previous studies using a block-design LFT have indicated that patients with schizophrenia have not only reduced activity, but also inappropriate activity timing, especially at the start of the task period and post-task period, compared with healthy controls (4, 5). Subsequently, the Joint Project

for Psychiatric Application of Near-Infrared Spectroscopy (JPSY-NIRS) Group has applied to these results and improved in the applicable way for clinical settings. The integral value (the size of the fNIRS signal area during the task period) and centroid value (the centroid time of the fNIRS signal area throughout the task) were determined by using averaged brain signals estimated in the frontopolar cortex. This group showed preliminarily that 69% of patients with MDD and 69% of patients with schizophrenia, and 69% MDD patients and 81% BP patients were correctly differentiated under an algorithm using these two values (10, 11). A part of these results was approved as one of the Advanced Medical Technologies as an aid for the differential diagnosis of depressive symptoms in 2009, which was the first such approval in the field of psychiatry in Japan (10, 11). Several criticisms have arisen regarding the limited replication in various clinical settings and the lack of consensus for application to mental health (77, 78). However, paper published recently on JPSY-NIRS replicated previous results (12). Using this algorithm, fNIRS can differentiate patients with depressive symptoms between major depressive disorder and psychotic disorders (bipolar disorder and schizophrenia), with a high classification rate (74.6 and 85.5%, respectively).

OTHER COGNITIVE TASKS AND MEASUREMENT SETTINGS

Three studies have explored the differences in brain activity during a random generation task (RNG) between patients with schizophrenia and healthy controls. Sinba et al. used a two-channel fNIRS instrument to describe for the first time that patients with schizophrenia had reduced brain activity in the PFC and worse task performances during the RNG compared with healthy controls, which represented different features during ruler-catching and sequential finger-to-thumb tasks (79). As healthy controls with better RNG task performances had greater brain activity, it remained unclear whether low brain activity was derived from worse task execution and/or functional impairment in schizophrenia. Hoshi et al. used time-resolved spectroscopy and two-channel fNIRS instruments to show that patients with schizophrenia, particularly those with a longer duration of illness, had reduced hemoglobin concentration during the resting state, and that this may cause altered activity during the RNG task (80). Koike et al. used a multi-channel fNIRS instrument to show that patients with schizophrenia had significantly reduced activity in the bilateral DLPFC and VLPFC regions, and that the activity in the right DLPFC region was associated with an earlier age at onset (81).

Okada et al. firstly showed the presence of altered brain activity in schizophrenia using a two-channel fNIRS instrument (62). Patients with schizophrenia had an aberrant task-related response pattern during a mirror drawing task, which was thought to be derived from a disrupted interhemispheric integration. Fallgatter et al. also showed the presence of altered frontal lateralization in schizophrenia during a continuous performance task using a two-channel fNIRS instrument (82). Folley et al. explored brain activity in patients with schizophrenia, individuals with schizotypal personality, and healthy controls during a divergent-thinking task using a two-channel fNIRS instrument, and showed that individuals with schizotypal personality had enhanced divergent-thinking ability and greater brain activity in the right PFC compared with patients with schizophrenia and healthy controls (83). Lee et al.

showed alternations in brain activity using fMRI and 24-channel fNIRS (not simultaneously) during the same event-related spatial working-memory task: patients with schizophrenia recruited the bilateral PFC, whereas healthy controls recruited only the right PFC (28). Zhu et al. used a 48-channel fNIRS instrument to show that patients with first-episode schizophrenia had reduced brain activity over the PFC during the Tower of London task (84). Nishimura et al. used a 52-channel fNIRS instrument during a go-no-go task to show that healthy controls had a significant decrease in activity in the DLPFC during the no-go condition, whereas patients with schizophrenia exhibited no changes (67). Furthermore, the high excitement score observed in patients with schizophrenia was associated with brain activity in the FPC and right DLPFC. Taniguchi et al. used a 24-channel fNIRS instrument to show that patients with schizophrenia had reduced brain activity in the PFC compared with healthy controls during a kana Stroop task, with similar task performances, whereas both patients and controls showed lack of activity during a kanji Stroop task, with significantly worse performance observed in the schizophrenia group (85).

Other than cognitive tasks, Fujita et al. explored hemoglobin changes through an electroconvulsive therapy using a two-channel fNIRS instrument, and showed that patients with schizophrenia had asymmetric hemoglobin changes in the PFC compared with patients with depression (86).

GENETIC VARIATION

Although schizophrenia is a syndrome, has been considered as a consolidation of several pathophysiological features, and has high genetic heritability, no crucial genetic risk factor has been found (87, 88). The results of genome-wide association studies that used a large sample size have suggested that schizophrenia risk genes are unable to be determined by specific gene variants but are thought to consist of common variants; furthermore, these risk genes had a substantial influence on environmental effects that occurred before the onset of schizophrenia. To clarify the impact of specific genes related to schizophrenia on the brain, imaging/genetics studies were performed to explore the relationship between brain structure and activity and genetic variants.

Five studies have explored the relationship between genetic variants and brain activity using fNIRS instruments. Takizawa et al. firstly reported that the val108/158met polymorphism of the catechol-*O*-methyltransferase (*COMT*) gene affected brain activity in the PFC only in schizophrenia patients (and not in healthy controls) (89). Schizophrenia patients with the Met variant (Val/Met and Met/Met) had significantly greater activation in the bilateral FPC and DLPFC during the LFT than did Val/Val carriers, implying that the inverted U curve shift of dopamine availability in schizophrenia might have an effect on the brain activity in the PFC (89). Regarding the Gln/Pro polymorphism of the sigma-1 receptor gene, Takizawa et al. reported that patients with the Gln/Gln genotype had significantly greater brain activity in the FPC and left DLPFC during the LFT than did Pro allele carriers; however, no significant differences were observed in healthy controls (90). However, Ohi et al. later used a two-channel fNIRS machine and a larger sample set to show that this genotype effect occurred in both the schizophrenia and control groups (91). Ohi et al. also reported

that individuals with a longer cytosine/adenine/guanine (CAG) repeat in the spinocerebellar ataxia type 17 gene had reduced activity in the bilateral PFC during the TOH task in both the schizophrenia and control groups (92). Regarding the rs41279104 polymorphism of the nitric oxide synthase-I gene, Reif et al. showed that patients who were A allele carriers had significantly reduced activity in the right PFC during a VFT compared with those who had the GG genotype (93).

As recent methodological progress in gene analysis allows the exploration of whole genetic alterations between cases and controls using more than 10,000 samples, imaging/genetics studies should be performed using methods that enable the analysis of numerical data sets, such as bioinformatics and machine learning methods (94). Conversely, the investigation of the relationship between brain activity and relevant target genes (e.g., DLPFC function under dopamine regulation and *COMT* variants) may provide another imaging/genetics study strategy. The analysis of altered gene function in the brain among psychiatric illnesses may clarify the pathophysiology of specific psychiatric disorders and identify new treatment options.

EFFECT OF MEDICATION ON BRAIN ACTIVITY

As previous clinical fNIRS studies have mostly explored patients in the chronic stage and receiving medication, the effect of medication on brain function was a limitation of these studies. Although an inconsistent effect of medication on fNIRS signal has been reported (68, 70, 71, 79), most previous fNIRS studies have reported an absence of association between brain activity and medication dose (3, 5, 12, 74, 81, 84–86) or different brain activity between individuals with ultra-high risk for psychosis with and without medication (3) (Table 1). However, all of those studies were cross-sectional, and a previous randomized and controlled trial showed that the administration of mirtazapine increased brain activity compared with trazodone and placebo in healthy volunteers (95). Controlled trials and/or longitudinal investigation to elucidate specific drug effects will be needed.

LIMITATIONS OF PREVIOUS STUDIES AND FURTHER DIRECTIONS

The previous fNIRS studies of schizophrenia had several limitations; therefore, we propose further directions for future investigation (Table 3). First, as most previous studies have performed cross-sectional measurements in chronic and stable patients receiving medication, symptomatic, and functional changes were not fully explored. As fNIRS is able to perform measurements relatively easily in unstable patients, such as those with acute or recurrent conditions, longitudinal studies aimed at investigating changes in clinical symptoms and social function will be needed (3, 96). Although previous studies have revealed a negligible medication effect on fNIRS signals, investigations of drug-naïve patients or of those receiving controlling treatment (e.g., specific drugs, electroconvulsive therapy, and neurofeedback) will be needed to allow further clinical applications of fNIRS (60, 86, 97). The use of the easy portability of fNIRS machines may allow measurements in earlier clinical stages in cohort settings, such as adolescents with psychotic-like experiences, which may reveal the alterations in brain development in the PFC (98).

Table 3 | Limitation of previous fNIRS studies and further implication.

Limitation of previous studies	Further implications
Cross-sectional measurement for chronic and stable patients with medication	Measure in different clinical stages (e.g., UHR, FEP, recurrent phase) Measure longitudinally to explore the relationship between clinical changes and fNIRS signals Measure in drug-naïve patients to explore drug effect Measure in a specific treatment response (e.g., medication, electroconvulsive therapy, neurofeedback) Measure in cohort setting (e.g., psychotic-like experiences)
One-sided task procedure (block-designed VFTs)	Use of other cognitive tasks Adopt event-related design Adopt more naturalistic task (e.g., driving, conversation)
Small sample size in single institute	Make consortium with the same instrument and measurement procedure (e.g., task paradigm, probe setting) Adopt more sophisticated analytical methods (e.g., measurement tools, bioinformatics, machine learning) Standardize manuscript description Construct fNIRS community

UHR, ultra-high risk; FEP, first-episode psychosis.

Second, half of the previous studies of schizophrenia adopted block-design VFTs for cognitive activation. Although one of the major disadvantages of fNIRS is the inability to measure brain activity in deep brain tissues, and the block-design VFT is appropriate for elucidating brain activity over the PFC, other cognitive tasks, and event-related design will be helpful to explore brain pathology in schizophrenia and to compare signal differences between fNIRS and other neuroimaging tools, such as fMRI and PET. Conversely, the exploration of brain activity in a more naturalistic position and during natural activities, such as driving and conversation, is suitable for future investigations using the advantages of fNIRS (99, 100).

Third, as fNIRS allows easy and repetitive measurements, a study including a large number of samples has been conducted (12). To analyze such a large data set, the same measurement procedure regarding task paradigm and probe setting and more sophisticated analytical methods, such as measurement tools (e.g., NIRS-SPM) (101), bioinformatics methods, and machine learning (94), will be needed. Standardized manuscript description and a database system will be needed for further comparisons and meta-analyses (102). The construction of an fNIRS community is expected to provide this type of background in NIRS research (18).

CONCLUSION

Functional near-infrared spectroscopy has been progressing rapidly in the field of psychiatry, as it provides several advantages, such as small size, portability, silent functioning, and the achievement of easy and non-invasive measurements. A part of these results was approved in 2009 as one of the Advanced Medical Technologies as an aid for the differential diagnosis of depressive symptoms (10–12), which was the first such approval in the field of psychiatry in Japan. Future investigations aimed at exploring fNIRS differences in various clinical stages, longitudinal changes, drug effects, and variations during different task paradigms will be needed to develop more accurate biomarkers that can be used to aid differential diagnosis, the comprehension of the present condition, the prediction of outcome, and the decision regarding treatment options in schizophrenia.

Future fNIRS research environments will require standardized measurement procedures, probe settings, analytical methods and tools, manuscript description, and database systems in a fNIRS community.

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