トを自動的に算出するものとして開発した。ADNI2のデータから、同一被験者の同一検査で撮像されたパラレルイメージング有りと無しの画像からこれらの指標を算出し、高速撮像によって画質の劣化（コントラストの低下）がないことを確認した。また、視認によるアーチファクトのチェックも行って、パラレルイメージングに特異的な大きなアーチファクトがないことも確認した。

ファントムは基準構造が同一の液体で満たされている直径が180mmと200mmのものを購入し、テスト撮像を開始した。

D. 考察

海外で先行している多施設脳画像研究の成果をベースに撮像方法の標準化がなされ、MRI を用いた気分障害の多施設共同研究体制が整った。また、これまで明確な指標のなかった原画像の品質管理法として定量性を持つ指標を提案し、装置間での画像品質の比較を可能とした。今後研究参加施設で収集されるデータを解析し、さらなる原画像および解析画像の品質管理法の開発を行うとともに、実際に脳体積計測を行い、気分障害の診断補助に有用な指標を見出していく予定である。

E. 結論

構造MRIを用いた気分障害の診断補助法開発の一環として、撮像プロトコルの標準化とファントム撮像および原画像の品質管理のためのプログラム開発を行った。次年度以降で標準化されたプロトコルによって撮像されたデータの解析を行い、画像品質管理プログラムのバリデーションを行うと共に脳形態解析結果の装置間差の詳細な検討を行う予定である。

F. 研究発表

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2. 学会発表

なし

G. 知的財産権の出願・登録状況（予定を含む）

1. 特許取得

該当なし

2. 実用新案登録

該当なし。

3. その他

該当なし

Ⅲ. 業績一覧

研究成果の刊行に関する一覧表

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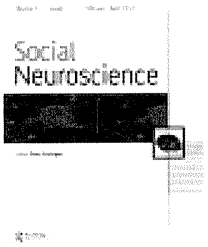
Ⅳ. 研究成果の刊行物・別刷



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Potential biomarker of subjective quality of life: Prefrontal activation measurement by near-infrared spectroscopy

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Potential biomarker of subjective quality of life: Prefrontal activation measurement by near-infrared spectroscopy

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Recently, there has been growing emphasis on enhancing subjective quality of life (QOL), in addition to treating symptoms or extending one's life. However, the neurobiological basis of subjective QOL is unknown. To illuminate the neural substrates that inform subjective QOL, the association between prefrontal function and subjective QOL was explored in 72 healthy volunteers (40 women and 32 men; age, 45.1 ± 20.1 y), using 52-channel near-infrared spectroscopy (NIRS), a portable neuroimaging device that can measure brain function in a less-constrained condition. Results confirmed that subjective QOL was positively correlated with prefrontal hemodynamic response during a cognitive task and that subjective satisfaction regarding social relationships and in the physical domains were cardinal contributors to the association. These findings suggest that subjective QOL has possible involvement in prefrontal function and that NIRS potentially plays a role as a biological marker of subjective QOL.

Keywords: Near-infrared spectroscopy (NIRS); Quality of life; Well-being; Satisfaction; Biological markers; Neuroimaging.

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In 1948, the World Health Organization (WHO) defined "health" as a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity (World Health Organization [WHO], 1948). Furthermore, the WHO defined "quality of life (QOL)" as the individual's perceptions in the context of their culture and value systems, in relation to their personal goals, standards, and concerns (Kuyken et al., 1995). Many questionnaires for measuring subjective QOL have been developed in the past. The questionnaires of subjective QOL are usually composed of multiple domains (e.g., physical function, bodily pain, mental health, anxiety/depression, vitality, activities, social relations, and self-care) (Harper & Power, 1998; Rabin & Charro, 2001; Ware & Sherbourne, 1992).

However, criticisms that standard subjective QOL measures are not person-centered and do not account for individual variation remain salient. The components of subjective QOL are varied and the weighting system for each component is not uniform among questionnaires (Carr & Higginson, 2001). In addition, individual differences in expectations for life influence subjective QOL (Carr, Gibson, & Robinson, 2001). Finally, subjective questionnaires have some inherent potential biases (Atkinson, Zibin, & Chuang, 1997; Donaldson & Grant-Vallone, 2002; Hebert et al., 1997).

In the clinical setting, it is important to improve both subjective QOL/well-being and the symptoms of the disease. Until recently in psychiatry, the established goal of therapy was "remission," defined as the improvement of symptoms (e.g., depressed mood, hallucinations, and delusions) (Frank et al., 1991; Pearlson et al., 1989). However, some psychological problems persist even after symptomatic improvement and even sub-threshold symptoms can trigger a rapid relapse (IsHak et al., 2011; Judd et al., 1998, 2000). In this context, subjective QOL or well-being has been recognized as a more pertinent outcome measure in recent years.

Several studies have examined the association between subjective QOL and neurocognitive function. Subjects with a higher subjective QOL index, measured by the Medical Outcomes Study (MOS) 36-item Short-Form Health Survey (SF-36), demonstrated better performance on the verbal fluency task (VFT) (Cohen et al., 1999). In a randomized clinical trial on training for cognitive function in older healthy adults without cognitive impairment, participants who received the intervention of processing speed training were significantly less likely to have declines in their QOL scores (SF-36) than participants who did not receive the intervention (Wolinsky et al., 2006). The prefrontal cortex is involved in the processing of various cognitive functions including, the VFT (Cabeza & Nyberg, 2000; Elfgren & Risberg, 1998) and speed of processing (Kochunov et al., 2010). Furthermore, previous neurophysiologic studies have examined the relationship between prefrontal function and indices similar to subjective QOL. In an electroencephalography (EEG) study of healthy subjects, increased prefrontal activity (greater on the left than on the right) in the resting state was associated with higher levels of well-being (Urry et al., 2004), an index that is often used synonymously with subjective QOL (Costanza et al., 2007; Gasper, 2010). A resting-state EEG study revealed robust relationships between left-side dominant asymmetry in the prefrontal cortex and positive affect (Tomarken, Davidson, Wheeler, & Doss, 1992), which was closely associated with life satisfaction (Emmons & Diener, 1985) and played a key role in shaping well-being (Urry et al., 2004). Another EEG study demonstrated that greater left frontal activation was associated with positive affect in response to a positive stimulus (Wheeler, Davidson, & Tomarken, 1993). These neurocognitive and EEG studies suggest that the prefrontal cortex plays a key role in shaping good subjective QOL.

Multi-channel near-infrared spectroscopy (NIRS) is a restraint-free, easy-to-use, portable, relatively inexpensive, and noninvasive functional-neuroimaging technology. NIRS can be used to detect the concentrations of oxyhemoglobin ([oxy-Hb]) and deoxyhemoglobin ([deoxy-Hb]), which are assumed to reflect the regional cerebral blood volume (rCBV). Previous NIRS studies using a variety of cognitive tasks have been reported (Koike et al., 2011; Nishimura et al., 2011). In particular, many of the studies investigated the VFT and prefrontal activation in healthy people (Herrmann, Ehlis, & Fallgatter, 2003; Kameyama, Fukuda, Uehara, & Mikuni, 2004) and decreased or abnormal prefrontal activation patterns in mood disorders (Herrmann, Ehlis, & Fallgatter, 2004; Kameyama et al., 2006; Matsuo, Kato, Fukuda, & Kato, 2000) and schizophrenia (Kubota et al., 2005; Suto, Fukuda, Ito, Uehara, & Mikuni, 2004; Takizawa et al., 2008) were repeatedly reported using NIRS.

Therefore, the hypothesis of this study was that the large prefrontal activation during VFT measured by NIRS was associated with good subjective QOL. To date, this is the first study to investigate the neurobiological basis of subjective QOL in healthy individuals. This study examines the relationship between the level of subjective QOL and the prefrontal hemodynamic response during VFT measured by NIRS in healthy adults.

METHODS

Participants

Seventy-two right-handed healthy volunteers (40 women and 32 men) participated in this study. All participants were recruited from the acquaintance of the authors and from the community through website advertisements. The average age was 45.1 y (range 16–71 y, standard deviation [SD] = 20.1 y). The mean IQ was 107.1 points (range 85.4–119.8 points, SD = 9.9 points) based on the Japanese version of the National Adult Reading Test (Matsuoka, Uno, Kasai, Koyama, & Kim, 2006). The exclusion criteria used in this study were neurological illness, traumatic brain injury with any known cognitive consequences or loss of consciousness for >5 min, previous alcohol/substance abuse or addiction, and a previous psychiatric disorder or a family history of psychotic disorders in their first-degree relatives. To rule out any psychiatric disorders, trained psychiatrists (K.K. and R.T.) examined all participants using the modified Mini-International Neuropsychiatric Interview (Otsubo et al., 2005; Sheehan et al., 1998). This study was approved by the ethics committee of the University of Tokyo Hospital (No. 630–6). All subjects gave written informed consent in accordance with the Declaration of Helsinki after a complete explanation of the study.

Clinical evaluation

The subjective QOL in each participant was assessed using the Japanese version of World Health Organization-Quality of Life-26 (WHOQOL-26/WHOQOL-BREF) (Harper & Power, 1998; Tazaki & Nakane, 1997). The WHOQOL-BREF measures the current subjective satisfaction of participants regarding their QOL on 26 items. Of the 26 items, 24 are divided into four categories, that is, physical domain, psychological domain, social relationships, and environment, and two items indicate their general impression of QOL. Each item is rated from 1 [*poor*] to 5 [*good*] and is presented as an average score.

Cognitive activation task

The 160-s block-designed VFT, which is well adapted to NIRS measurement, was used as a cognitive activation task (Takizawa et al., 2008, 2009). During the 60-s task period, a participant was instructed to say as many words aloud as possible. The initial phonological syllable was given from a computer. The 60-s task period was divided into three continuous 20-s sub-periods and the initial syllables were changed so that the participant avoided silence (first,/to/,/a/, or/na/; second,/i/,/ki/, or/se/; third,/ta/,/o/, or/ha/). During the 30-s pre-task and 70-s post-task periods, the participant was instructed to say Japanese vowels (/a/,/i/,/u/,/e/, and/o/) aloud repeatedly as a control and to remove pronunciation-related brain activation and task-related motion artifacts. The total number of correct words the participant generated during the task period was recorded as his/her task performance.

NIRS measurement

The 52-channel NIRS machine (ETG-4000, Hitachi Medical Co., Japan) measures relative changes of [oxy-Hb] and [deoxy-Hb] at the surface of the cortex using two wavelengths (695 and 830 nm) of near-infrared light based on the modified Beer–Lambert law (Yamashita et al., 1996). The NIRS probes were fixed with thermoplastic shells (3 rows by 11 columns) and the probe interval was set at 3.0 cm, with the lowest probes positioned along the T4-Fpz-T3 line according to the international 10–20 system used in EEG. This probe arrangement measures [Hb] in the bilateral prefrontal (approximately dorsolateral [Brodmann's area (BA) 9, 46], ventrolateral [BA 44, 45, 47], and frontopolar [BA 10]) and superior temporal cortical surface regions. The correspondence between the probe positions and the measurement areas on the cerebral cortex was confirmed based on a previous multisubject study of anatomical craniocerebral correction via the international 10–20 system (Okamoto et al., 2004; Tsuzuki et al., 2007).

The time resolution of NIRS was set at .1 s. As the NIRS signal was sometimes unstable at the start of the pre-task, the pre-task baseline was determined as the mean across the last 10 s of the pre-task period and the post-task baseline was determined as the mean across the last 10 s of the post-task period. Then, a linear fitting method was performed using the two baselines. NIRS signals were sensitive to physiologic activities such as the systemic arterial pulse oscillations (–1 Hz) and respiration (.2–.3 Hz) (Hoshi, 2003). Thus, moving average methods were applied to remove short-term changes (moving average window: 5 s). Grand mean waveforms averaged across subjects were created separately for each type of [Hb]. Because the moving average methods could not be used to correct all artifacts, a fully automatic rejection of data with artifacts was performed separately for each channel according to the computer algorithm

for quantitatively evaluating artifacts (Takizawa et al., 2008).

Statistical analysis

For data analysis using parametric statistical tests, [Hb] data from each channel were averaged across the task period. Since [oxy-Hb] changes were assumed to more directly reflect cognitive activation than [deoxy-Hb] changes, as previously shown in animal studies and in correlation with fMRI (Hoshi, Kobayashi, & Tamura, 2001; Strangman, Culver, Thompson, & Boas, 2002), this study focused on [oxy-Hb].

For each of the 52 channels to confirm the significant activations, the mean [oxy-Hb] changes from pre-task baseline to the activation period were compared using a paired Student's *t*-test. As 52 paired *t*-tests were performed, the false discovery rate (FDR) correction method was used to correct for multiple comparisons (two-tailed; maximum FDR = .05, such that on average, no more than 5% false positives were found) (Singh & Dan, 2006).

Pearson's correlation coefficients were calculated for a relationship between the mean [oxy-Hb] changes during the task period and the average of the total scores of WHOQOL-BREF for each channel (using FDR correction method). Since WHOQOL-BREF is an ordinal scale, we preliminarily examined the distribution normality of the average of the total scores of WHOQOL-BREF using the Shapiro–Wilk test ($p > .05$). For the channels with significant correlation between the mean [oxy-Hb] changes and the average of the total scores of WHOQOL-BREF, we performed stepwise multiple regression analyses to investigate the relationship between VFT performance and the mean [oxy-Hb] change and to confirm the relationship even if potential confounding factors (i.e., age, gender, and estimated IQ) were controlled. Hence, we used the mean [oxy-Hb] changes as the dependent variable and the average of the total scores of WHOQOL-BREF, VFT performance, age, gender (dummy parameterized, female = 0, male = 1), and estimated IQ as the independent factors.

In order to clarify what kind of subjective QOL contributes to the relationship between subjective QOL and prefrontal activation, stepwise multiple regression analyses were also conducted for the significant correlation coefficients between the mean [oxy-Hb] change and the average of the total scores of WHOQOL-BREF. The mean [oxy-Hb] changes during the task in each channel were analyzed as a dependent variable. Five subcategories of the WHOQOL-BREF (physical domain, psychological domain, social relationships, environment, and general QOL impression) served as independent variables. All analyses were performed using IBM SPSS Statistics (SPSS) 19 (IBM, Armonk, NY USA).

RESULTS

The grand average of the average of the total scores of WHOQOL-BREF was 3.74 (SD = .44) and the average scores for the physical health domain, psychological health domain, social relationship domain, environment domain, and general QOL impression were 3.81 (SD = .49), 3.66 (SD = .56), 3.74 (SD = .49), 3.75 (SD = .48), and 3.63 (SD = .66), respectively. The average of the number of words generated during the VFT was 15.1 (SD = 4.2). The mean [oxy-Hb] change during the activation period was larger than that during the pre-task baseline at all 52 channels (FDR correction method; $p < .006$; Figure 1).

There were significant positive correlations between the mean [oxy-Hb] changes and the average of the total scores of WHOQOL-BREF in 13 channels (CH 3, 14, 15, 17, 18, 25, 27, 28, 37–39, 45, and 48; $r = .25–.44$, $p < .05$). Among these channels, six channels survived FDR correction (CH 17, 18, 27, 28, 38, and 48; $r = .33–.44$; $p < .005$); (Figure 2). These six channels were localized in the left prefrontal region (CH 17, 27, 38, and 48 were congruent with the left middle frontal gyrus and CH 18 and 28 with the left inferior frontal gyrus) (Tables 1 and 2) by using a virtual registration method (Shattuck et al., 2008; Takizawa et al., 2013; Tsuzuki & Dan, 2013).

The multiple regression analysis also revealed significant relationships in these six channels between the mean [oxy-Hb] changes and the average of the total scores of WHOQOL-BREF ($R^2 = .15–.27$, adjusted $R^2 = .14–.25$, beta = .26–.42, $p < .05$) after controlling for other potential confounding factors. The contribution of VFT performance to the mean [oxy-Hb] changes in these six channels was not significant. Significant relationships were found in gender for three channels (CH 17, 27, 28; $R^2 = .16–.24$, adjusted $R^2 = .14–.22$, beta = .21–.24, $p < .05$) and age for one channel (CH 38, $R^2 = .27$, adjusted $R^2 = .25$, beta = –.37, $p < .05$) (Table 1).

In order to confirm the influence of the five subcategories of the WHOQOL-BREF, multiple regression analysis was performed on the six channels with significant [oxy-Hb] changes. In each multiple regression analysis, significant regression was obtained in all six channels. The selected variables were physical domain

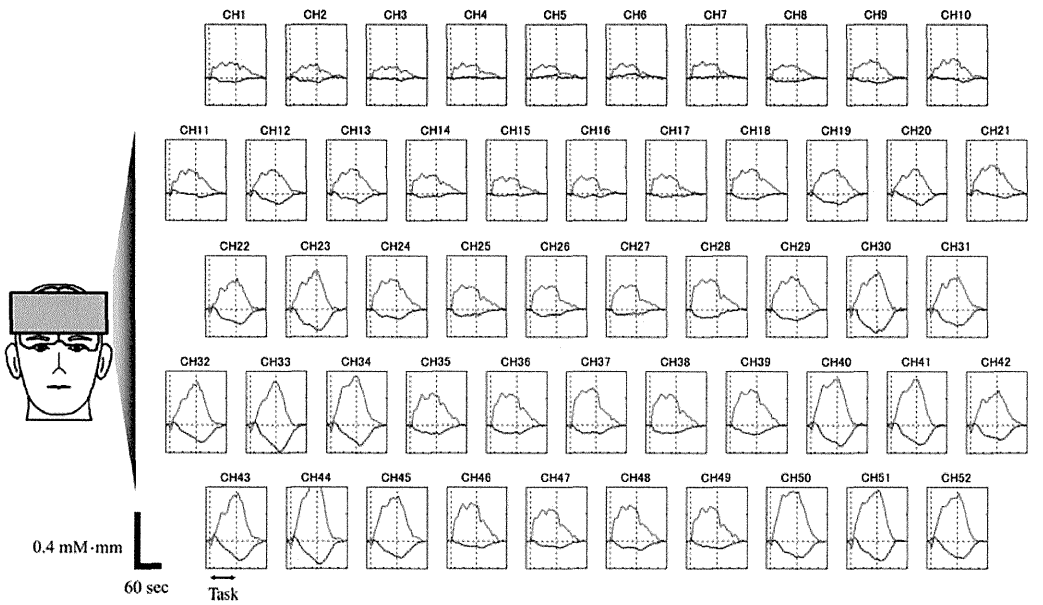

Figure 1. Grand average waveforms of hemoglobin concentration ([Hb]) changes during the verbal fluency task (VFT) across all the subjects for every channel. [oxyHb] and [deoxyHb] are shown in red and blue, respectively. The arrow between the two vertical lines indicates the VFT activation period. [Hb] changes were corrected for the effect of simple speaking by using linear fitting between the pre-task baseline (the initial 10 s of the time course shown in the graphs) and the post-task baseline (the last 10 s).

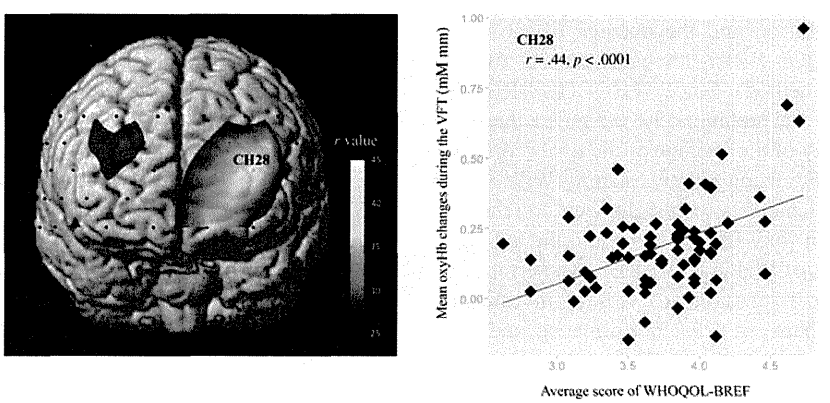

Figure 2. (Left) Cerebral mapping illustrating a significant positive correlation between the mean [oxy-Hb] changes and the average score on the WHOQOL-BREF ($p < .05$). Six channels survived FDR correction. (Right) The graphs show a scatter plot of a typical significant channel in the prefrontal cortex (CH28).

score (CH 17, 27, 28, 38, 48; beta = .28–.40, $p < .05$) and social relationship score (CH 18, 28; beta = .31–.48, $p < .05$) (Table 2).

DISCUSSION

To our knowledge, this is the first study to directly examine the association between subjective QOL and prefrontal activation using NIRS. The characteristics of NIRS as a portable neuroimaging device that can measure brain hemodynamic response under a less-constrained condition may have advantage in finding an association with subjective QOL in an individual's social life in the community. The results of this study showed that [oxy-Hb] changes during the VFT in the prefrontal and anterior temporal regions were significantly greater than baseline in healthy people. The [oxy-Hb] changes during the VFT in the prefrontal region was positively correlated with the average of

TABLE 1
Stepwise multiple regression analysis based on the average score of WHOQOL-BREF, demographic variables (age, gender, and estimated IQ), and task performance

			Independent variables[a]		
			The average of the total scores of WHOQOL-BREF		*Others*
Channel No.	R^2	*Adjusted* R^2	*Beta*	p	
Left middle frontal gyrus					
CH 17	.18	.15	.32	.004	Gender[b]: beta = .24, p = .030
CH 27	.16	.14	.31	.006	Gender[b]: beta = .23, p = .046
CH 38	.27	.25	.26	.021	Age: beta = –.37, p = .001
CH 48	.16	.14	.39	.001	
Left inferior frontal gyrus					
CH 18	.15	.14	.39	.001	
CH 28	.24	.22	.42	.000	Gender[b]: beta = .21, p = .047

Notes: Dependent variable: the mean [oxy-Hb] changes during the task period. [a]In the sequence in which they entered the regression equation. [b]Female = 0, male = 1.

TABLE 2
Stepwise multiple regression analysis based on the five subcategories of the WHOQOL-BREF (physical domain, psychological domain, social relationships, and environment and general impression of QOL)

Channel No.	*Independent variables*[a] *(subcategories of the WHOQOL-BREF)*				
	R^2	*Adjusted* R^2		*Beta*	p
Left middle frontal gyrus					
CH 17	.16	.15	Physical domain	.40	.000
CH 27	.15	.14		.39	.001
CH 38	.14	.13		.37	.001
CH 48	.14	.13		.38	.001
Left inferior frontal gyrus					
CH 18	.23	.22	Social relationship	.48	.000
CH 28	.26	.24	Physical domain	.28	.023
			Social relationship	.31	.011

Notes: Dependent variable: the mean [oxy-Hb] changes during the task period. [a]In the sequence in which they entered the regression equation.

the WHOQOL-BREF total score even after controlling for VFT task performance and confounding demographic factors. The relationship between VFT performance and the mean [oxy-Hb] changes in these regions was not significant. In addition, the [oxy-Hb] changes during the VFT were primarily associated with subjective satisfaction in social relationships and the physical domain in the WHOQOL-BREF.

Our results revealed a positive relationship between prefrontal hemodynamic response during VFT by NIRS and subjective QOL. Previous research suggested a relationship between neurocognitive function that was involved with prefrontal cortex and subjective QOL (Cohen et al., 1999; Wolinsky et al., 2006). In some EEG studies, it was shown that well-being (Urry et al., 2004) and positive affect (Tomarken et al., 1992), which were similar concepts to subjective QOL (Costanza et al., 2007; Emmons & Diener, 1985; Gasper, 2010), were related to prefrontal function. We obtained similar results and this suggests an important role of prefrontal function in shaping subjective QOL. However, the underlying mechanism is not clear.

The prefrontal cortex has extensive connections with other cortical and subcortical regions (Arnsten, 2009) and serves the function of regulating attention, thought, and action (Goldman-Rakic, 2011); inhibiting inappropriate actions (Aron, Robbins, & Poldrack, 2004); regulating emotion (Price & Amaral, 1981); and error monitoring (Modirrousta & Fellows, 2008). Although the entire picture of prefrontal function remains enigmatic, it is thought that these higher-order cognitive abilities are responsible, at least in part, for performing effective daily activities. Burgess and colleagues noted that the high-level of executive control associated with the prefrontal region is likely to be a vital component of everyday life (Burgess, Veitch, de Lacy Costello, & Shallice, 2000) and Wise described that prefrontal areas contribute collectively to behaviors particularly important to our lives (Wise, 2008). Considering these contexts, it may be reasonable to speculate that the function of the prefrontal area as a whole of several elemental functions affects day-to-day life and that prefrontal function measured by NIRS was related with subjective QOL, a comprehensive index. It is also possible that stress involves the relationship between subjective QOL and prefrontal function. Some studies showed that subjective QOL was improved by stress reduction intervention (Nyklicek & Kuijpers, 2008; Reibel, Greeson, Brainard, & Rosenzweig, 2001). These previous results suggest a close relationship between stress and subjective QOL. On the other hand, it was indicated that stress exposure caused loss of prefrontal cognitive abilities and architectural changes in prefrontal dendrites (Arnsten, 2009). Thus, the degree of stress, which is intimately associated with subjective QOL, might influence prefrontal function.

With regard to the association between subjective QOL and prefrontal function, subjective satisfaction regarding social relationships, which is a subcategory

of the WHOQOL-BREF, was an important factor in this study. In recent studies in monkeys, prefrontal function showed a significant association with the social network or social state (Fujii, Hihara, Nagasaka, & Iriki, 2009; Sallet et al., 2011). The evolution of the prefrontal cortex may be an essential factor in the development of social relationships in primates. Furthermore, a clinical study on patients after brain injury described the association between prefrontal cortex damage and social perception (Mah, Arnold, & Grafman, 2004). These findings suggest that the prefrontal cortex plays an important role in social relationships. However, further research is needed to shed light on the neural mechanisms of subjective satisfaction in social relationships.

In addition, among subcategories of the WHOQOL-BREF, subjective satisfaction in the physical domain was a large factor in the prefrontal hemodynamic responses during VFT. Pioneering neuropsychological or neuroimaging studies have shown that the prefrontal cortex is responsible for subjective evaluation of physical state, such as sleep (Suda et al., 2008), pain (Apkarian et al., 2004; Lorenz, Minoshima, & Casey, 2003), and fatigue (Morgan et al., 2007; Suda et al., 2009), which are items included in the physical domain of the WHOQOL-BREF (i.e., pain and discomfort, dependence on medicinal substances and medical aids, energy and fatigue, mobility, sleep and rest, activities of daily living, and work capacity). Moreover, many previous studies have reported that physical exercise has an influence on brain function and affects physical satisfaction (Thøgersen-Ntoumani, Fox, & Ntoumanis, 2005). Studies have shown that physical exercise, during a defined period of time, improved performance on a neuropsychological test related to prefrontal function (Harada, Okagawa, & Kubota, 2004; Stroth et al., 2010). In an fMRI study, it was documented that physical exercise increased prefrontal task-related brain activation (Colcombe et al., 2004).

Additionally, it is necessary to consider the possibility that the meaning of brain activation amount (high or low) varies based on task type and load. For example, it was indicated that there was a positive correlation of the error rate with prefrontal activation during a high-load working memory task (Ito et al., 2011). In working memory and decision-making processes, the magnitude of prefrontal activation increased with the workload to some degree; however, further increased workload decreased activation because of less effortful processing (Bunce et al., 2011). On the other hand, previous research using the VFT in the same way described here found no correlation between VFT performance and prefrontal activation (Kameyama et al., 2006; Noda et al., 2012; Sawa et al., 2013). In these tasks, the assigned syllables were changed every 20 s during the 60-s task period in the VFT to decrease the time during which the subjects were silent so that it was easier for subjects to produce the words (Kameyama et al., 2006). Accordingly, it is possible that prefrontal activation was not influenced by the VFT performance. Furthermore, in these previous studies, subjects with milder depressive symptoms showed larger activation during the task (Sawa et al., 2013), and the activation during the task was larger in healthy subjects than in those with major depressive disorder (Noda et al., 2012) or bipolar disorder (Kameyama et al., 2006). Considering these observations, larger prefrontal activation during the VFT adopted in our study was estimated to indicate the normality or goodness of prefrontal function. That is, our results suggest a positive correlation between normal or good prefrontal function and high subjective QOL.

The results of the present study must be viewed in light of its limitations. NIRS detects brain activation only from focused areas of the cortical surface and cannot detect signals from other brain structures. There is a possibility that deeper brain functions (cf, anterior cingulate cortex or amygdala), together with the prefrontal region, are involved in subjective QOL or other similar indices (i.e., well-being and positive affect) (Abercrombie et al., 1998; Schaefer et al., 2002; van Reekum et al., 2007). For a more detailed understanding, comprehensive research on other regions, including the deeper brain regions, would be necessary. Since this was a cross-sectional study, a causative relationship between good prefrontal function and high subjective QOL could not be determined. Furthermore, whether good prefrontal function confers a high subjective QOL, or stress that reflects subjective QOL influences prefrontal function cannot be determined. Longitudinal studies are necessary to clarify this question. Finally, in the present study, the WHOQOL-BREF was used to evaluate subjective QOL. However, there are many other subjective QOL measurement tools that contain other components. There are also various definitions of wellness and there is no explicit consensus on the definition of subjective QOL (Gasper, 2010). Since these concepts have not been universally defined within the field, future research would require a complete and thorough discussion of what QOL encompasses and how to evaluate that.

CONCLUSION

This study demonstrated a positive correlation between subjective QOL and VFT-related prefrontal hemodynamic responses measured using NIRS. These results indicate that subjective QOL involves prefrontal function and suggests potential availability of NIRS to evaluate subjective QOL, which is one of the most critical outcomes in clinical settings.

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Genetic influences on prefrontal activation during a verbal fluency task in adults: A twin study based on multichannel near-infrared spectroscopy

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ABSTRACT

Near-infrared spectroscopy (NIRS) studies have reported that prefrontal hemodynamic dysfunction during executive function tasks may be a promising biomarker of psychiatric disorders, because its portability and noninvasiveness allow easy measurements in clinical settings. Here, we investigated the degree to which prefrontal NIRS signals are genetically determined. Using a 52-channel NIRS system, we monitored the oxy-hemoglobin (oxy-Hb) signal changes in 38 adult pairs of right-handed monozygotic (MZ) twins and 13 pairs of same-sex right-handed dizygotic (DZ) twins during a letter version of the verbal fluency task. Heritability was estimated based on a classical twin paradigm using structured equation modeling. Significant genetic influences were estimated in the right dorsolateral prefrontal cortex and left frontal pole. The degrees of heritability were 66% and 75% in the variances, respectively. This implies that the prefrontal hemodynamic dysfunction observed during an executive function task measured by NIRS may be an efficient endophenotype for large-scale imaging genetic studies in psychiatric disorders.

Abbreviations: DZ, dizygotic; FIQ, full-scale intelligence quotient; LFT, Letter Fluency Task; MZ, monozygotic; NIRS, near-infrared spectroscopy; rCBV, regional cerebral blood volume; SES, socioeconomic status; SNP, single nucleotide polymorphism; WAIS-R, Wechsler Adult Intelligence Scale-Revised; [oxy-Hb], concentration of oxyhemoglobin; [deoxy-Hb], concentration of deoxyhemoglobin.

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Introduction

It is well known that there is a substantial genetic influence in major psychiatric disorders, such as schizophrenia and bipolar disorder. The identification of endophenotypes in psychiatric disorders is becoming an increasingly pressing matter in the elucidation of their genetic underpinnings (Gottesman and Gould, 2003). An endophenotype is a type of biomarker that is both associated with a specific psychiatric disorder and is genetically influenced. Endophenotypes are thought to link complicated pathways from genotypes to phenotypes.

Event-related potentials, such as P50, P300, and mismatch negativity, have been investigated as candidate endophenotypes of schizophrenia and other psychiatric conditions (Bramon et al., 2004; Hall et al., 2006; Umbricht and Krljes, 2005). Working memory and executive performance are also thought to contribute to the psychopathology of schizophrenia. Abnormal functioning of the dorsolateral prefrontal cortex was found not only in patients with schizophrenia, but also in their unaffected siblings (Callicott et al., 2003). More recently, several functional magnetic resonance imaging (fMRI) studies revealed a genetic contribution to prefrontal blood oxygenation level-dependent (BOLD) signal changes in response to a working memory task (Blokland et al., 2008, 2011; Koten et al., 2009). These findings support the contention that such characteristics in cognitive neuroscience might serve as an endophenotype of schizophrenia.

Multichannel near-infrared spectroscopy (NIRS) is a functional neuroimaging modality that enables the noninvasive detection of the concentrations of oxyhemoglobin ([oxy-Hb]) and deoxyhemoglobin ([deoxy-Hb]), which are assumed to reflect the regional cerebral blood volume (rCBV). NIRS is suitable for clinical application, particularly in psychiatric disorders, because it has a relatively low cost, is easy to set up, the subject can be examined in a natural sitting position, and its measurements are relatively insensitive to motion artifacts (Takizawa et al., 2008).

NIRS studies using the letter version of the verbal fluency task (LFT) as a cognitive activation task have revealed an LFT-related increase in prefrontal [oxy-Hb] among healthy subjects (Herrmann et al., 2003; Kameyama et al., 2004). Frontal-task-related NIRS signals are being vigorously investigated as potential clinically applicable biomarkers. Decreased or abnormal LFT-related brain activation was found among patients with a variety of psychiatric disorders, including schizophrenia (Kubota et al., 2005; Suto et al., 2004; Takizawa et al., 2008) and mood disorders (Herrmann et al., 2004; Kameyama et al., 2006; Matsuo et al., 2000). Individuals with pervasive developmental disorders (Kuwabara et al., 2006) and their unaffected siblings (Kawakubo et al., 2009) also showed a decreased hemodynamic response compared with individuals with typical development.

Several previous studies also reported that polymorphisms in the catechol-O-methyltransferase (*COMT*) and sigma-1 receptor genes were associated with the variations in prefrontal hemodynamic response observed among patients with psychiatric disorders, such as schizophrenia (Takizawa et al., 2009a,b) and panic disorder (Tanii et al., 2009). Those results imply that there are genetic influences on prefrontal activation as measured by NIRS.

In the present study, we investigated the heritability of LFT-related prefrontal hemodynamic responses, as measured by NIRS, in healthy twins using a conventional twin study paradigm. To our knowledge, this is the first twin NIRS study to further our understanding of the genetic contribution to the variation in brain function, which might deepen our interpretation of individual differences in brain processing and vulnerability to brain disorders.

Materials and methods

Participants

This study was performed as a part of a large-scale neuroimaging study on healthy twins (Todai-TWIN). Fifty-one same-sex twin pairs who had been reared together (102 participants) were recruited via newspaper advertisements and participated in the study. All participants were right-handed according to the Edinburgh Inventory (Oldfield, 1971) and were native Japanese speakers. Twins were screened for significant medical conditions, traumatic brain injuries with loss of consciousness for more than 5 min, current use of medication that was likely to affect cognition, history of neurological and psychiatric disorders, history of alcohol and illicit drug abuse, and family history of axis I psychiatric disorders in their first-degree relatives. The zygosity of 76 twin pairs (74.5%) was confirmed genetically. To do this, DNA extracted from peripheral leukocytes was genotyped using the Genome-Wide Human SNP Array 6.0 (Affymetrix, Santa Clara, CA). The zygosity of the remaining twin pairs was determined using a questionnaire composed of 3 questions that can be used to diagnose zygosity with more than 90% accuracy (Ooki et al., 1990). These analyses revealed that 38 pairs were monozygotic (MZ) (35 females and 3 males) and 13 pairs were dizygotic (DZ) (12 females and 1 male).

Socioeconomic status (SES) was assessed using the Hollingshead scale (Hollingshead, 1957). Full-scale intelligent quotient (FIQ) was estimated using the short version of the Japanese Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Misawa et al., 1993; Wechsler, 1981). The distance between T3 and T4 along the scalp was measured and considered as the index of head size. The demographic data are summarized in Table 1. All twins were scanned on the same day as their cotwins. The ethics committee of the Faculty of Medicine, the University of Tokyo, approved this study (No. 630-(6) & 2450-(2)).

Activation task

Participants were asked to seat themselves on a chair with their eyes open and to minimize bodily movements throughout the NIRS measurements. The procedure of cognitive activation was the same as that used in previous studies (Nishimura et al., 2009; Takizawa et al., 2008), which included a 30-s pre-task baseline, a 60-s verbal fluency task (letter version), and a 70-s post-task baseline (Fig. 1). Prepared vocal instructions were given to the participants during the procedure. During the pre-task and post-task periods, the subjects were instructed to repeat a train of Japanese vowels (/a/, /i/, /u/, /e/, and /o/). This was intended to prevent task-unrelated contemplation and to record brain activities due to vocalization. During the verbal fluency task period, participants were instructed to generate as many Japanese words beginning with a given syllable as possible. The initial syllables were changed every 20 s during the 60-s task period, to reduce wordless time. The responses generated by the participants were assessed, and the number of correct words generated was defined as a measure of task performance.

NIRS measurements

Relative changes in [oxy-Hb] and [deoxy-Hb] were measured using 695 nm and 830 nm wavelengths of near-infrared light. The 52-channel NIRS machine (ETG-4000, Hitachi Medical Co.) used in this study included 16 emitter probes and 15 detector probes that were fixed alternately with thermoplastic 3 × 11 shells, which constitutes 52 adjacent emitter–detector probe pairs separated by 3.0 cm (henceforth termed "channel (Ch)"). These probes were placed over a subject's bilateral prefrontal regions so that the lowest 11 probes were located along the Fp1–Fp2 line according to the international 10–20 system in electroencephalography. This arrangement of the probes can measure [oxy-Hb] and [deoxy-Hb] from bilateral prefrontal and superior temporal cortical surface regions (Fig. 2). For the purpose of estimating the cortical localization of each channel, the use of the virtual registration method (Tsuzuki et al., 2012; Tzourio-Mazoyer et al., 2002) enabled the probabilistic registration of NIRS data onto the Montreal Neurological Institute (MNI) coordinate space without measurement of probe positions or the use of MRI (Fig. 2). The placement of the emitter and detector probes on the scalp at a distance of 3.0 cm from each other enables the detection of [Hb]