Relation between working memory performance and evoked cerebral blood oxygenation changes in the prefrontal cortex evaluated by quantitative time-resolved near-infrared spectroscopy

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Objectives: The lateral prefrontal cortex (LPFC) plays a central role in working memory (WM). In the present study, we employed quantitative, near-infrared time-resolved spectroscopy (TRS) to evaluate the relation between LPFC activity during WM and the task performance in 19 healthy, middle-aged, female subjects (mean age of 46.8±2.1 years).

Methods: Concentration changes of oxyhemoglobin (oxy-Hb), deoxyhemoglobin, and total hemoglobin in the bilateral LPFC were measured by means of TRS during performance of Sternberg tests (ST) of one digit and six digits. The oxy-Hb changes were compared to performance in ST. In addition, we evaluated whether pathlength of the forehead and baseline concentration of oxy-Hb influenced WM performance.

Results: TRS revealed increases in oxy-Hb in association with a decrease in deoxy-Hb during ST. We found a significant negative correlation between the reaction time of six-digit ST and oxy-Hb changes in the bilateral LPFC (left, $P=0.0061$; right, $P=0.0029$); however, no significant correlation was observed with one-digit ST. In contrast, accuracy of ST did not correlate with the oxy-Hb changes in the prefrontal cortex. The optical pathlength of the forehead and concentration of oxy-Hb at rest in the LPFC did not correlate with either reaction time or accuracy in ST.

Conclusion: The present results indicate that oxy-Hb changes in the LPFC during a WM task, as measured by TRS, correlated with WM performance. TRS is compact and less expensive than functional magnetic resonance imaging, and may be a useful tool to evaluate neural correlates of WM in normal adults.

Keywords: Prefrontal cortex, Sternberg test, Time-revolved spectroscopy, Working memory

Introduction

Working memory (WM) is a system for actively maintaining and manipulating information, and forms an integral part of the human memory system. Neuroimaging studies on WM, using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), have revealed that the lateral prefrontal cortex (LPFC) plays a central role in WM.[1–3] In addition, it has been demonstrated that the activation pattern of the LPFC induced by WM tasks changes during aging-associated decline in WM performance; older adults tend to exhibit a reduction in the hemispheric lateralization (i.e. reduced asymmetry) of activation observed in younger adults.[4,5] Although these studies provided precise information about the neural networks involved in WM, fMRI and PET require complicated procedures and large facilities, and have high running costs.

Near-infrared spectroscopy (NIRS) is a non-invasive optical technique that detects neuronal metabolic activity by measuring evoked cerebral blood oxygenation (CBO) changes; NIRS allows calculation of the concentration changes of oxyhemoglobin (oxy-Hb) and deoxyhemoglobin (deoxy-Hb) in cerebral compartments based on measurement of the absorption spectra of hemoglobin (Hb) in the near-infrared range.[6] NIRS is compact and less expensive than fMRI or PET. In addition, NIRS can be measured in more natural environment where the head restraint is not required. Consequently, NIRS measurements are less stressful, which is important for the evaluation of cognitive function.

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We and others have demonstrated that NIRS is a useful tool to evaluate brain function in normal adults[7–12] and patients with brain disorders.[13–20]

A number of NIRS studies on WM have demonstrated a positive correlation between LPFC activity and behavioral performance in WM tasks.[21–26] That is, subjects with shorter reaction times had greater increases in oxy-Hb in the LPFC.[21,22] It should be noted, however, that the NIRS instrument in those studies employed continuous wave (CW) light and calculated Hb concentration changes based on the modified Beer–Lambert law. Therefore, the obtained values are the product of concentration changes and the optical pathlength, which CW-NIRS cannot measure. In contrast, near-infrared time-resolved spectroscopy (TRS), employing pico-second light pulses, enables us to determine the mean optical pathlength, thereby allowing the calculation of quantitative values of Hb concentration changes in the region through which the near-infrared light passes. In addition, TRS allows measurement of baseline concentration of Hb at the resting condition,[26] through application of the photon diffusion equation.[27] The quantitative accuracy of TRS has been established.[28,29] Sakatani *et al.* employed a two-channel TRS system, which has high time resolution, to evaluate the evoked CBO changes in the LPFC during cognitive tasks, and demonstrated that the TRS system allows real-time measurements of both activation and deactivation caused by a language task and driving simulation, respectively.[30–32]

In the present study, we investigated whether LPFC activity during a WM task, measured by the two-channel TRS system, predicts WM performance. We measured evoked CBO changes in the LPFC during Sternberg tests (ST) by means of TRS, and evaluated the relation between changes in oxy-Hb and reaction time and accuracy of the test. In addition, we evaluated whether pathlength of the forehead and baseline concentration of Hb at rest, measured by TRS, affect the relation between the evoked CBO changes and WM performance. Finally, we discussed the usefulness and limitations of quantitative assessment of evoked CBO changes by TRS in the diagnosis of WM impairment.

Experimental Procedure

Subjects

We studied a total of 19 healthy young female subjects (mean age of 46.8 ± 2.1 years). The subjects were highly educated college students, and were all deemed right-handed according to the laterality quotient questionnaire of the Edinburgh Handedness Inventory. Potential subjects who self-reported a substance abuse problem or other psychiatric disorder were excluded from the study. All subjects provided written informed consent as required by the Human Subjects Committee of the Shiseido Life Science Institute.

WM task and psychological studies

We employed the modified ST as a WM task.[23] In the ST, subjects were asked to remember one digit and six digits by turns. There were eight one-digit trials and eight six-digit trials. Each trial began with the presentation of one digit or a set of six digits to be encoded for 1 second on CRT. Then a blank display 3 was inserted for 2 seconds, followed by the test digit until a response was obtained within 2 seconds. Subjects held a small box with two buttons side by side. They were required to press the right button if they thought the test digit was contained within the encoded stimulus and to press the left one if not, as quickly and accurately as possible. Similar tasks have been used previously in NIRS experiments and have been demonstrated to activate the LPFC.[23]

TRS measurements of LPFC activity

We measured CBO in the bilateral LPFC with a two-channel NIRS monitor which uses time-resolved reflectance spectroscopy (TRS-20; Hamamatsu Photonics K.K., Hamamatsu, Japan). Details of this system have been described.[30,31] Briefly, it consists of three pulsed laser diodes with different wavelengths having duration of 100 ps at a repetition frequency of 5 MHz, a photomultiplier tube, and a circuit for time-resolved measurement based on the time-correlated single photon counting method. The observed temporal profiles were fitted into the photon diffusion equation[27] using the non-linear least-squares fitting method. The concentrations of oxy-Hb, deoxy-Hb, total Hb (=oxy-Hb+deoxy-Hb; t-Hb) and cortical oxygen saturation ($CoSO_2$) were calculated using the least-squares method. The concentrations of Hb were expressed in μM.

The NIRS probes were set symmetrically on the forehead, so that the midpoint between the emission and detection probes was 3 cm above the centers of the upper edges of the bilateral orbital sockets; the distance between the emitter and detector was set at 4 cm. Magnetic resonance imaging confirmed that the emitter–detector was located over the dorsolateral and frontopolar areas of the PFC.[11]

Data analysis

The evoked CBO changes in the bilateral LPFC were continuously monitored by TRS and were averaged every second during: (1) baseline conditions for 60 seconds; (2) ST for 60–80 seconds (the period varied according to each subject's reaction time); and (3) recovery for 60 seconds. To analyze LPFC activity in response to WM performance, we calculated changes in oxy-Hb concentration during ST since these reflect changes in neuronal activity.[7–16,18–26]

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The mean baseline values (measured during 60 seconds) were subtracted from the mean activation values (measured during the first 60 seconds under task performance).

We evaluated the difference in concentrations of Hb and optical pathlength at rest in the right and left LPFC; two-way analysis of variance was conducted with and within-subject factors of task (average Hb values before and during ST) and hemisphere (left and right). In addition, we evaluated the correlation between performance of ST (i.e. reaction time and accuracy) and concentrations of oxy-Hb and optical pathlength in the LPFC using Spearman's rank correlation.

Results

Table 1 shows average values of Hb concentrations and optical pathlength in the bilateral frontal regions at rest in all subjects. There were no significant differences in Hb concentrations and optical pathlength between the right and left LPFC.

Figure 1A shows a typical example of evoked CBO response during ST measured by TRS; the task increased oxy-Hb and decreased dexoy-Hb. There were significant task effects in oxy-Hb ($F=7.08$, $P<0.05$) and deoxy-Hb ($F=4.70$, $P<0.05$); however, there was no significant effect in t-Hb ($F=1.78$, $P=0.20$). Figure 1B shows average concentration changes of oxy-Hb, dexoy-Hb, and t-Hb during ST in the bilateral prefrontal cortex. There were no significant effects and interactions according to the hemisphere for Hb concentration changes.

We found a significant negative correlation between the reaction time of six-digit ST and oxy-Hb changes in the left ($P=0.0061$) and right ($P=0.0029$) LPFC (Fig. 2). The reaction time in the subjects who exhibited a decrease in oxy-Hb (1117.3 ± 172.4 milliseconds, $n=13$) in the right LPFC was significantly longer than that of the subjects who exhibited an increase in oxy-Hb (891.2 ± 156.3 milliseconds, $n=6$, $P=0.016$) in the right LPFC.

In contrast, accuracy of ST did not correlate with the oxy-Hb changes in the LPFC. Finally, the concentration of oxy-Hb at rest and the optical pathlength did not correlate with the reaction time of ST ($P>0.05$).

Table 1 Concentrations of hemoglobin and optical pathlength at rest in the right and left LPFC

	oxy-Hb (μM)	deoxy-Hb (μM)	t-Hb (μM)	OP (cm)
R-LPFC	38.0±5.6	19.4±3.7	57.4±8.7	26.0±2.6
L-LPFC	38.2±6.1	19.1±2.9	57.3±8.6	26.1±2.6

Note: LPFC=lateral prefrontal cortex; oxy-Hb=oxyhemoglobin; deoxy-Hb=deoxyhemoglobin; t-Hb=total hemoglobin; OP=optical pathlength, R=right; L=left.

Discussion

In the present study, we found a significant negative correlation between oxy-Hb changes during ST in the LPFC and the reaction time of six-digit ST, indicating that ST-induced LPFC activity is positively correlated with performance of WM. The results obtained by TRS are consistent with the previous CW-NIRS studies on WM.[21–26] It has been demonstrated that subjects with shorter reaction times had higher levels of oxy-Hb concentration in the LPFC during performance of a modified Stroop paradigm.[21,22] Tsujii *et al.* evaluated the effect of H_1-receptor antagonists on the LPFC activity induced by ST task.[23] They found that subjects who received a sedative first-generation H_1-receptor antagonist exhibited longer reaction times and smaller increases in oxy-Hb during the task in the LPFC compared to those who received a second-generation H_1-receptor antagonist or placebo.[23,24,33]

The findings obtained by CW-NIRS, however, could be a consequence of possible differences in optical pathlength in the subjects and/or changes of optical pathlength during neuronal activity. In the present study, employing TRS, we found no correlation between optical pathlength and reaction time of ST. In addition, previous TRS studies revealed no significant changes in optical pathlength of the forehead during cognitive tasks.[30,31] These observations indicate that the optical characteristics of the recording region did not affect the value of the evoked CBO change. Furthermore, the concentration of oxy-Hb at rest in the LPFC exhibited only small differences among subjects, and did not correlate with reaction time in ST. These observations strongly suggest that the LPFC activity induced by ST is positively correlated with performance in ST.

ST caused increases in oxy-Hb in the bilateral LPFC; there was no significant difference in oxy-Hb changes induced by ST between the right and left LPFC. It has been reported that WM tasks caused asymmetrical activation in LPFC in younger adults, while older adults tended to exhibit a reduction in hemispheric lateralization (i.e. reduced asymmetry). For example, in tasks associated specifically with left LPFC activation in younger adults, such as verbal WM and semantic encoding, older adults often show both left and right LPFC.[4,5,34,35] This phenomenon is called HAROLD (hemispheric asymmetry reduction in older adults).[4] Dixit *et al.*, employing PET, demonstrated occurrence of HAROLD prior to age 50.[35] These results, obtained by both PET and TRS, suggest that reduction in asymmetry could occur at ages prior to the fifties. Further studies are necessary to investigate the time course and physiological mechanism of HAROLD.

In the present study, we observed a decrease in oxy-Hb during ST in 13 subjects. The decreases in

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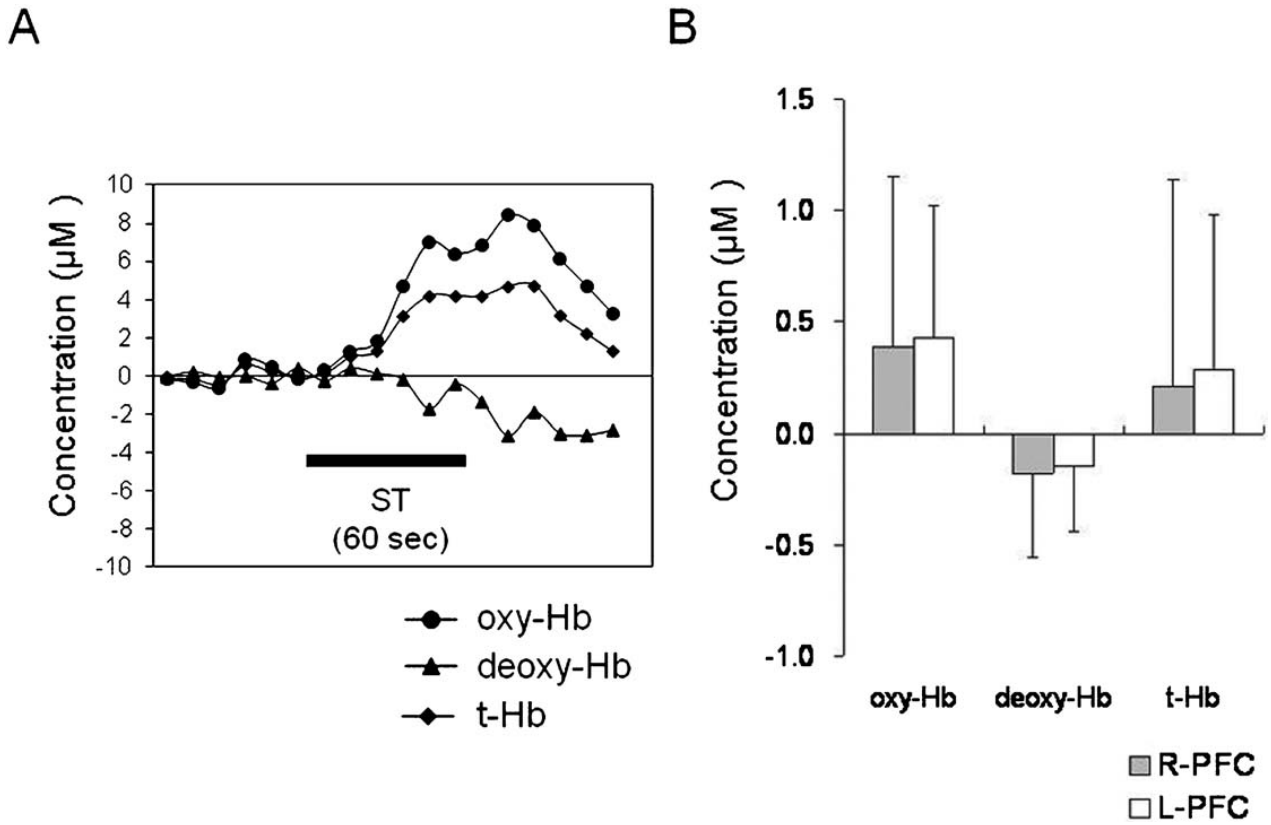

Figure 1 (A) Typical examples of evoked cerebral blood oxygenation changes in the lateral prefrontal cortex during Sternberg test (ST). Note that oxyhemoglobin (oxy-Hb) increased in association with a decrease in deoxyhemoglobin (deoxy-Hb). The ordinate represents the change in concentration of oxy-Hb (filled circle), deoxy-Hb (filled triangle), and total hemoglobin (t-Hb; filled square) in μM. The thick bar denotes the performance period (60 seconds) of ST. (B) Average concentration changes of oxy-Hb, dexoy-Hb, and t-Hb during ST in the bilateral prefrontal cortex. The ordinate represents the change in concentration of Hb. There were no significant effects and interactions according to the hemisphere for Hb concentration changes.

oxy-Hb implied a decrease in regional cerebral blood flow in response to the task, suggesting that the task caused deactivation in the PFC. The physiological mechanism of deactivation in the PFC during ST remains unclear. However, the following mechanisms warrant consideration. First, a stealing of blood from less active regions into the most cerebral blood flow-demanding area could induce deactivation.[36] Second, a suppression of neuronal activities could reduce the regional cerebral blood flow. Raichle *et al.* proposed that such a reduction in neuronal activities might be mediated through the action of diffuse projecting systems like dopamine or a reduction in thalamic inputs to the cortex during attention-demanding cognitive tasks.[37] Further studies are necessary to investigate the mechanism of a decrease in oxy-Hb during ST.

It has been reported that a multi-channel TRS system could image activation areas in the LPFC during cognitive tasks.[32,38] Although the TRS used in the present study was only a two-channel system, it has several advantages compared to a multi-channel system. First, the two-channel system is quite simple, which is advantageous in a clinical setting. Indeed, placement of the optodes of a multi-channel system requires more time than that of a two-channel system. Second, two-channel data acquisition has no need for statistical corrections for multiple comparison as does multi-channel data acquisition. Third, subjects may feel pain at the scalp with multi-channel systems, but this has not been reported with the two-channel system, and therefore the quality of the PFC recording may be better in the latter case. Particularly in patients with impaired cognitive function, it is difficult to place the optodes of a multi-channel system on the scalp. Indeed, we and others have demonstrated the usefulness of the two-channel system for evaluation of neural correlates of cognitive function in the LPFC.[10–12,14–16,18–20] Finally, it should be noted that the Hb concentrations measured by TRS are the average concentrations within the illuminated area, including the extracranial and intracranial tissues. At present, it is difficult to measure the Hb concentrations in the brain tissue selectively.

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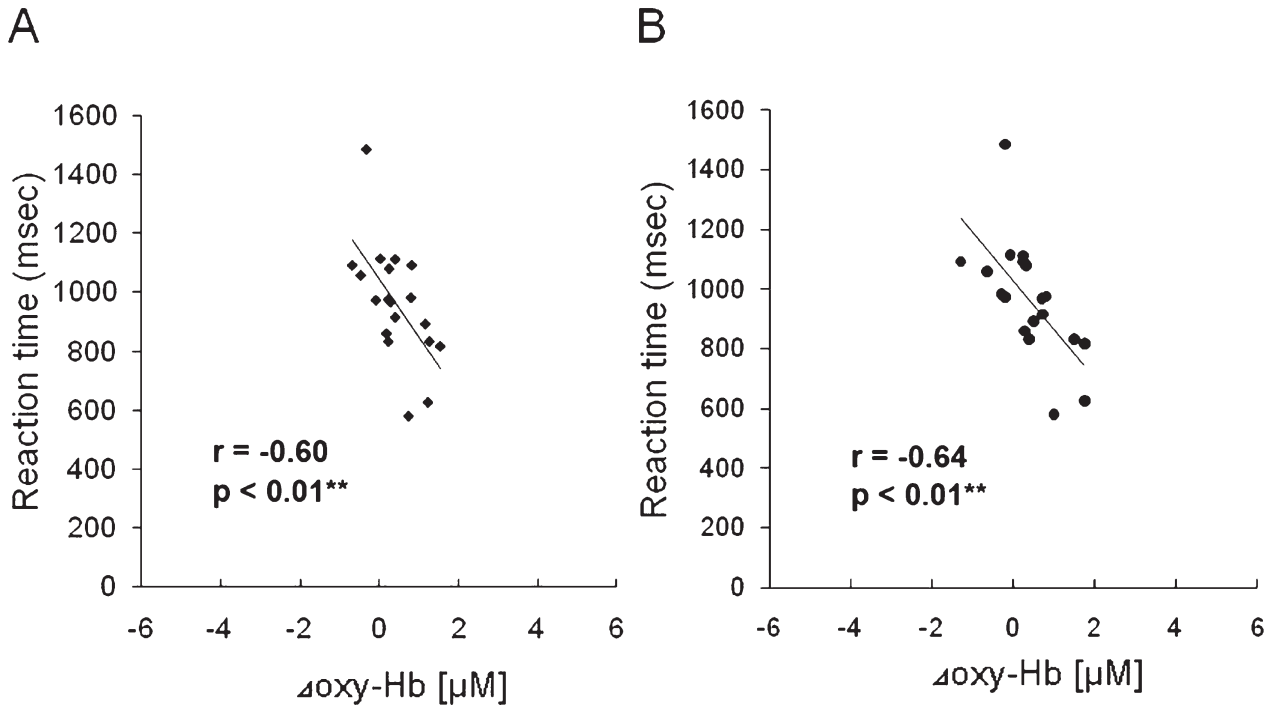

Figure 2 Relation between the reaction time of six-digit Sternberg test (ST) and oxyhemoglobin (oxy-Hb) changes in the left (A) and right (B) lateral prefrontal cortex (LPFC). There was a significant negative correlation between the reaction time of six-digit ST and oxy-Hb changes in the left (P=0.0061) and right (P=0.0029) LPFC. The ordinate represents the reaction time of ST (millisecond), while the abscissa represents the change in oxy-Hb concentration (μM).

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References

1 Passingham D, Sakai K. The prefrontal cortex and working memory: physiology and brain imaging. Curr Opin Neurobiol 2004;14:163–8.
2 D'Esposito M, Aguirre GK, Zarahn E, Ballard D, Shin RK, Lease J. Functional MRI studies of spatial and nonspatial working memory. Brain Res Cogn Brain Res 1998;7:1–13.
3 Hoshi Y, Tsou BH, Billock VA, Tanosaki M, Iguchi Y, Shimada M, *et al*. Spatiotemporal characteristics of hemodynamic changes in the human lateral prefrontal cortex during working memory tasks. NeuroImage 2003;20:1493–504.
4 Cabeza R. Hemispheric asymmetry reduction in older adults: the HAROLD model, Psychol Aging 2002;17:85–100.
5 Cabeza R, Daselaar SM, Dolcos F, Prince SE, Budde M, Nyberg L. Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. Cereb Cortex 2004;14:364–75.
6 Jobsis FF. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science 1977;198:1264–7.
7 Herrmann MJ, Ehlis AC, Fallgatter AJ. Frontal activation during a verbal-fluency task as measured by near-infrared spectroscopy. Brain Res Bull 2003;61:51–6.
8 Tsujii T, Watanabe S. Neural correlates of dual-task effect on belief-bias syllogistic reasoning: a near-infrared spectroscopy study. Brain Res 2009;1287:118–25.
9 Tsujii T, Watanabe S. Neural correlates of belief-bias reasoning under time pressure: a near-infrared spectroscopy study. Neuroimage 2010;50:1320–6.
10 Tanida M, Sakatani K, Takano R, Tagai K. Relation between asymmetry of prefrontal cortex activities and the autonomic nervous system during a mental arithmetic task: near infrared spectroscopy study. Neurosci Lett 2004;369:69–74.
11 Tanida M, Katsuyama M, Sakatani K. Relation between mental stress-induced prefrontal cortex activity and skin conditions: a near infrared spectroscopy study. Brain Res 2007;1184:210–6.
12 Tanida M, Katsuyama M, Sakatani K. Effects of fragrance administration on stress-induced prefrontal cortex activity and sebum secretion in the facial skin. Neurosci Lett 2008;432:157–61.
13 Fallgatter AJ, Roesler M, Sitzmann L, Heidrich A, Mueller TJ, Strik WK. Loss of functional hemispheric asymmetry in Alzheimer's dementia assessed with near-infrared spectroscopy. Cogn Brain Res 1997;6:67–72.
14 Fujiwara N, Sakatani K, Katayama Y, Murata Y, Hoshino T, Fukaya C, *et al*. Evoked-cerebral blood oxygenation changes in false-negative activations in BOLD contrast functional MRI of patients with brain tumors. NeuroImage 2004;21:1464–71.
15 Ikezawa K, Iwase M, Ishii R, Azechi M, Canuet L, Ohi K, *et al*. Impaired regional hemodynamic response in schizophrenia during multiple prefrontal activation tasks: a two-channel near-infrared spectroscopy study. Schizophr Res 2009;108:93–103.
16 Kameyama M, Fukuda M, Yamagishi Y, Sato T, Uehara T, Ito M, *et al*. Frontal lobe function in bipolar disorder: a multichannel near-infrared spectroscopy study. Neuroimage 2006;29:172–84.
17 Murata Y, Sakatani K, Hoshino T, Fujiwara N, Kano T, Nakamura S, *et al*. Effects of cerebral ischemia on evoked cerebral blood oxygenation responses and BOLD contrast functional MRI in stroke patients. Stroke 2006;37:2514–20.
18 Sakatani K, Lichty W, Xie Y, Li S, Zuo H. Effects of aging on language-activated cerebral blood oxygenation changes of the left prefrontal cortex: near infrared spectroscopy study. J Stroke Cerebrovasc Dis 1999;8:398–403.
19 Sakatani K, Katayama Y, Yamamoto T, Suzuki S. Cerebral blood oxygenation changes of the frontal lobe induced by direct electrical stimulation of thalamus and globus pallidus: a near infrared spectroscopy study. J Neurol Neurosurg Psychiatry 1998;67:769–73.
20 Sakatani K, Xie Y, Lichty W, Li S, Zuo H. Language-activated cerebral blood oxygenation and hemodynamic changes of the left prefrontal cortex in poststroke aphasic patients: a near infrared spectroscopy study. Stroke 1998;29:1299–304.
21 Len-Carrion J, Damas-Lpez J, Martín-Rodríguez JF, Domínguez-Roldán JM, Murillo-Cabezas F, Barroso Y Martin JM, *et al*. The hemodynamics of cognitive control: the level of concentration of oxygenated hemoglobin in the superior prefrontal cortex varies as a function of performance in a modified Stroop task. Behav Brain Res 2008;193:248–56.

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The Charlesworth Group, Wakefield +44(0)1924 369598 - Rev 7.51n/W (Jan 20 2003)

22 Schroeter ML, Zysset S, Kupka T, Kruggel F. Near-infrared spectroscopy can detect brain activity during a color-word matching Stroop task in an event-related design. Hum Brain Mapp 2002;17:61–71.
23 Tsujii T, Yamamoto E, Ohira T, Saito N, Watanabe S. Effects of sedative and non-sedative H1 antagonists on cognitive tasks: behavioral and near-infrared spectroscopy (NIRS) examinations. Psychopharmacology 2007;194:83–91.
24 Tsujii T, Yamamoto E, Ohira T, Takahashi T, Watanabe S. Antihistamine effects on prefrontal cortex activity during working memory process in preschool children: a near-infrared spectroscopy (NIRS) study. Neurosci Res 2010;67:80–5.
25 Tsujii T, Yamamoto E, Masuda S, Watanabe S. Longitudinal study of spatial working memory development in young children. Neuroreport 2009;20:759–63.
26 Yokose N, Sakatani K, Murata Y, Awano T, Igarashi T, Nakamura S, *et al*. Bedside assessment of cerebral vasospasms after subarachnoid hemorrhage by near infrared time-resolved spectroscopy. Adv Exp Med Biol 2010;662:505–11. 4
27 Patterson MS, Chance B, Wilson C. Time resolved reflectance and transmittance for the non-invasive measurement of tissue optical properties. Appl Opt 1986;28:2331–6.
28 Delpy DT, Cope M, van der Zee P, Arridge S, Wray S, Wyatt J. Estimation of optical pathlength through tissue from direct time of flight measurement. Phys Med Biol 1988;33:1433–42.
29 Owen AW. The functional organization of working memory processes within human lateral frontal cortex: the contribution of functional neuroimaging. Eur J Neurosci 1997;9:1329–39.
30 Sakatani K, Yamashita D, Yamanaka T. Changes of cerebral blood oxygenation and optical pathlength during activation and deactivation in the prefrontal cortex measured by time-resolved near infrared spectroscopy. Life Sci 2006;78:2734–41.
31 Murata Y, Sakatani K, Hoshino T, Fujiwara N, Katayama Y, Yamashita D, *et al*. Changes of evoked cerebral blood oxygenation and optical pathlength in the frontal lobe during language tasks: a study by multi-channel, time-resolved near-infrared spectroscopy and functional MRI. Adv Exp Med Biol 2010;662:213–8.
32 Quaresima V, Ferrari M, Torricelli A, Spinelli L, Pifferi A, Cubeddu R. Bilateral prefrontal cortex oxygenation responses to a verbal fluency task: a multichannel time-resolved near-infrared topography study. J Biomed Opt 2005;10:11012.
33 Tsujii T, Masuda S, Yamamoto E, Ohira T, Akiyama T, Takahashi T, *et al*. Effects of sedative and nonsedative antihistamines on prefrontal activity during verbal fluency task in young children: a near-infrared spectroscopy (NIRS) study. Psychopharmacology (Berl) 2009;207:127–32.
34 Tsujii T, Okada M, Watanabe S. Effects of aging on hemispheric asymmetry in inferior frontal cortex activity during belief-bias syllogistic reasoning: a near-infrared spectroscopy study. Behav Brain Res 2010;210:178–83.
35 Dixit DK, Gerton BK, Dohn P, Meyer-Lindenberg A, Berman KF. Age-related changes in rCBF activation during an N-back working memory paradigm occur prior to age 50. NeuroImage 2000;11(Suppl 1):S94.
36 Harel N, Lee SP, Nagaoka T, Kim DS, Kim SG. Origin of negative blood oxygenation level-dependent fMRI signals. J Cereb Blood Flow Metab 2002;22:908–17.
37 Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci USA 2002;98:676–82.
38 Hoshi Y, Oda I, Wada Y, Ito Y, Yutaka Y, Oda M, *et al*. Visuospatial imagery is a fruitful strategy for the digit span backward task: a study with near-infrared optical tomography. Brain Res Cogn Brain Res 2000;9:339–42.

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