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Neuroscience Letters 369 (2004) 69–74
Neuroscience Letters
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Relation between asymmetry of prefrontal cortex activities and the autonomic nervous system during a mental arithmetic task: near infrared spectroscopy study

Masahiro Tanida[a,*], Kaoru Sakatani[b], Ruriko Takano[c], Keiko Tagai[c]

[a] Bioengineering Research Laboratories, Shiseido Life Science Research Center, 2-2-1 Hayabuchi, Tsuzuki-ku, Yokohama 224-8558, Japan
[b] Department of Neurological Surgery, Nihon University School of Medicine, Tokyo, Japan
[c] Shiseido Institute of Beauty Science, Tokyo, Japan

Received 12 April 2004; received in revised form 22 June 2004; accepted 23 July 2004

Abstract

The present study evaluated the relationship between asymmetry of the prefrontal cortex activity and the automatic nervous system (ANS) response during a mental arithmetic (MA) task. Employing near infrared spectroscopy, we compared cerebral blood oxygenation changes in the right and left prefrontal cortices during a mental arithmetic task with HR changes. During the MA task, eight subjects (high-HR group) showed large HR increases (14.2 ± 3.0) while eight subjects (low-HR group) showed small HR increases (3.6 ± 2.8) ($P < 0.00001$). In both the high-HR and low-HR groups, near infrared spectroscopy (NIRS) demonstrated increases of oxyhemoglobin and total hemoglobin (=oxyhemoglobin + deoxyhemoglobin) associated with decreases of deoxyhemoglobin in the bilateral prefrontal cortices during MA task. In the high-HR group, the laterality ratio scores, i.e., [(R − L)/(R + L) of oxyhemoglobin and total hemoglobin], showed positive values (0.17 ± 0.11 and 0.17 ± 0.17, respectively), while in the low-HR group, the laterality ratio scores showed negative values (−0.28 ± 0.21 and −0.35 ± 0.24, respectively). In addition, there were significant positive correlations between HR changes and the laterality ratio scores of oxyhemoglobin ($r = +0.87$, $P < 0.0001$) and total hemoglobin ($r = +0.85$, $P < 0.0001$). These results indicate that the MA task-induced activity in the right prefrontal cortex was larger than that in the left prefrontal cortex in the subject with high HR increases, suggesting that the right prefrontal cortex activity during the MA task has a greater role in cerebral regulation of HR by virtue of decreasing parasympathetic effects or increasing sympathetic effects.

Keywords: Prefrontal cortex activities; Autonomic nervous system; Near infrared spectroscopy; Hemispheric asymmetry; Mental arithmetic task

Several studies have demonstrated that the cerebrum plays an important role in regulation of the autonomic nervous system (ANS), and such cerebral regulation may be differentially mediated by the right and the left cerebrum. For example, electrical stimulation of the left insular cortex during neurosurgical operations decreases heart rate (HR) and systemic blood pressure, while right insular cortex stimulation causes increases in HR and systemic blood pressure [25]. Unilateral hemispheric inactivation by intracarotid amobarbital injection revealed that HR increased after left hemisphere inactivation, but decreased following right hemisphere inactivation [8]. In addition, power spectral analysis of HR during selective sensory stimulation of the hemispheres demonstrated a left hemisphere predominance in the control of parasympathetic modulation of HR [36]. These findings suggest that the left hemisphere predominantly modulates parasympathetic effects, while the right hemisphere predominantly modulates sympathetic effects of the ANS.

Electroencephalographic (EEG) studies have shown that greater right frontal activation was associated with increases in HR or blood pressure during unpleasant emotional stim-

* Corresponding author. Tel.: +81 45 590 6387; fax: +81 45 590 6078.
E-mail address: masahiro.tanida@to.shiseido.co.jp (M. Tanida).

0304-3940/$ – see front matter
doi:10.1016/j.neulet.2004.07.076

uli [30,35]. In addition, neuroimaging studies have revealed that the right frontal cortex, particularly the prefrontal cortex, was predominantly activated during negative emotional states (see review in Davidson and Irwin [4] and Fischer et al. [6]). These results imply that the right frontal cortex dominates sympathetic activity during stress-inducing mental tasks including emotional stimuli. However, the findings obtained by various investigations are contradictory. In several neuroimaging studies, no clear lateralization or functional role of the frontal cortex in ANS regulation during stress-inducing mental tasks was observed [2,31,32].

In the present experiment, we employed near infrared spectroscopy (NIRS) to evaluate the prefrontal cortex activity during a mental arithmetic (MA) task. NIRS is a noninvasive optical technique that can measure concentration changes of oxyhemoglobin (Oxy-Hb) and deoxyhemoglobin (Deoxy-Hb) in the cerebral vessels by means of the absorption spectra of hemoglobin in the near infrared range [18]. Changes in total hemoglobin (Total-Hb) (Oxy-Hb + Deoxy-Hb = Total-Hb) indicate blood volume changes, and changes in Oxy-Hb correlate with cerebral blood flow (CBF) changes under conditions of constant hematocrit [14]. Thus, NIRS allows the characterization of real-time changes in cerebral blood oxygenation (CBO) and CBF during neuronal activity, although NIRS cannot measure CBO changes in the subcortical structures, and its spatial resolution is poor as compared fMRI and PET. NIRS activation studies have demonstrated that cognitive tasks generally cause increases of Oxy-Hb and Total-Hb associated with decreases of Deoxy-Hb in the prefrontal cortex [12,13,15–17,28,29]. Such evoked-CBO changes are consistent with the results of a previous PET activation study [7]. In the present investigation, in order to assess the relation between asymmetry of the prefrontal cortex activities and the ANS, we measured the evoked-CBO changes in the right and left prefrontal cortices during an MA task using NIRS, and we compared the evoked-CBO changes and the HR changes during the task.

Sixteen healthy female subjects (aged 20–23 years; mean 21.4 years) participated in the present study. They were all right-handed as judged by the Edinburgh Handedness Inventory. To avoid the influence of environmental stress, the subjects were seated in a comfortable chair in a regular room with good air conditioning throughout the experiments.

We employed the MA task to activate the prefrontal cortex, since MA tasks have been used previously in various activation studies on the prefrontal cortex, including NIRS studies [15,16,17]. The subjects were asked to subtract serially a 2-digit number from a 4-digit number (e.g., 1022-13) as quickly as possible for 60 s.

Employing a photo-electrical sensor (Tuyama MGF Co., Tokyo, Japan), we monitored HR continuously during the experiment. The sensor was placed on the right earlobe of the subjects to measure the pulse wave. From its mean frequency value between 0.05 and 2 Hz by Fourier analysis, the instantaneous HR was calculated every 10 s.

We measured the evoked-CBO changes using a NIRO-300 (Hamamatsu Photonics K.K., Japan), which was used in our previous NIRS activation studies [9,23,24,27]. The near-infrared light from four laser diodes was directed at the head through a fiber-optic bundle, and the reflected light was transmitted to a multi-segment photodiode detector array [20]. Concentration changes of Oxy-Hb, Deoxy-Hb, and Total-Hb were continuously analyzed and were expressed in arbitrary units. The sampling time was 0.5 s. The center between the emitter and detector was identical to the Fp2 position of the international EEG 10–20 system used in the previous studies. MRI demonstrated that the emitter–detector was placed over the frontal lobe, mainly the prefrontal cortex [15].

NIRS is based on the modified Beer–Lambert law in which changes in hemoglobin chromophore concentrations are assumed to be proportional to changes in light absorbance divided by the extinction coefficients of the chromophores and the optical pathlength in the tissue, which is the average distance that light travels between the source and detector through the tissue [5]. For the measurement of absolute values of the hemoglobin chromophore concentration changes, it is necessary to determine the optical pathlength. In many activation studies employing continuous wave NIRS, such as the NIRO-300 in the present study, the values of NIRS parameters were compared among the subjects, based on the assumption that the optical pathlength is constant among each subject [33]. However, using a time-resolved NIRS, Zhao et al. [38] reported that the optical pathlength varied with the individual subjects, regions of the head, and wavelength. In a preliminary experiment, therefore, we measured the optical pathlength of the right and left foreheads in five healthy adults (mean age 32.4 year) employing the time-resolved NIRS (TRS-10, Hamamatsu Photonics K.K., Japan). The results demonstrated that there was no significant difference in pathlength between the right and left forehead (17.6 ± 1.2 and 17.7 ± 1.4, respectively; $P > 0.05$), indicating that the values for Oxy-Hb, Deoxy-Hb, and Total-Hb changes measured by the NIRO-300 could be compared between the right and left prefrontal cortices in the examined subjects.

NIRS data were converted into a digitized format via the multi-purpose analyzing program BIMTAS II (Kissei Comtec Co. Ltd., Japan). The data were averaged every second and the length of baseline measurements was normalized according to a 140-s segment for each trial. Each subject was made to perform under three kinds of experimental conditions during continuous measurement of the evoked-CBO changes: (1) control conditions for 20 s; (2) the MA task for 60 s; and (3) the recovery phase for 60 s.

We analyzed the changes in NIRS parameters (Oxy-Hb, Deoxy-Hb, and Total-Hb) by subtracting the mean control values (during the first 10 s) from the mean activation values (during the whole periods of the task). To evaluate the asymmetry of the Oxy-Hb and Total-Hb changes in the right and left prefrontal cortices, we calculated laterality ratio scores (i.e., [(right − left)/(right + left), changes of Oxy-Hb and Total-Hb]), which have been employed in the evaluation of

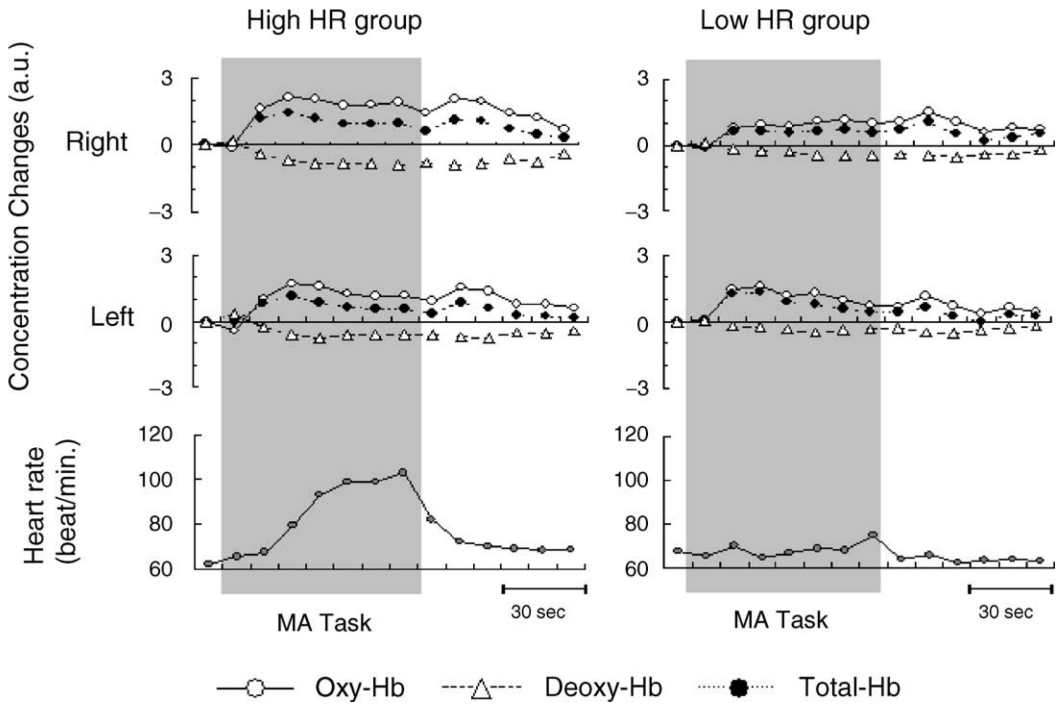

Fig. 1. Typical examples of changes in NIRS parameters and heart rate (HR) during mental arithmetic task in subjects with high HR increases (high-HR group) and low HR increases (low-HR group). The ordinate of NIRS parameters indicates the concentration changes of Oxy-Hb, Deoxy-Hb, and Total-Hb in arbitrary units. The ordinate of HR indicates number of beats per minutes. The gray area denotes the task period (60 s).

asymmetrical EEG activities during emotional stimuli [3]. Positive laterality ratio scores indicate that the increases of Oxy-Hb and Total-Hb in the right prefrontal cortex are larger than those in the left prefrontal cortex, while negative scores indicate a reverse relationship. The laterality ratio scores and HR changes were compared using Pearson's correlation coefficient and Student's *t*-test.

The baseline HR varied among the subjects, with values of between 90 and 60 beats/min. After the subjects had begun to perform the MA task, the HR was generally increased and reached peak levels within 30 s, and then returned to the baseline levels after the MA task. However, eight subjects (high-HR group) showed large HR increases (14.2 ± 3.0), while eight subjects (low-HR group) showed small HR increases (3.6 ± 2.8) ($P < 0.00001$).

In both the high-HR and low-HR groups, NIRS demonstrated increases of Oxy-Hb and Total-Hb associated with decreases of Deoxy-Hb in the bilateral prefrontal cortices during the MA task. These changes gradually returned to the control levels after the task. Interestingly, in the high-HR group, the increases of Oxy-Hb and Total-Hb in the right prefrontal cortex were greater than those in the left prefrontal cortex, while in the low-HR group, the increases were greater in the left prefrontal cortex than in the right prefrontal cortex. Fig. 1 presents examples of the NIRS parameters and HR changes during the task in these two groups.

In the high-HR group, the laterality ratio scores for Oxy-Hb and Total-Hb showed positive values (0.17 ± 0.11 and 0.17 ± 0.17, respectively), while in the low-HR group, the laterality ratio scores showed negative values (−0.28 ± 0.21 and −0.35 ± 0.24, respectively). Table 1 compares the laterality ratio scores for Oxy-Hb and Total-Hb in the high-HR and low-HR groups. Finally, we evaluated the correlation between the HR changes and the laterality ratio scores for Oxy-Hb and Total-Hb (Fig. 2). Significant positive correlations were noted for both Oxy-Hb ($r = +0.87$, $P < 0.0001$) and Total-Hb ($r = +0.85$, $P < 0.0001$).

The present investigation is the first NIRS activation study to assess the relationship between evoked-CBO changes and the ANS response. We compared the evoked-CBO changes in the right and left prefrontal cortices during an MA task. When evaluating these data, the following limitations of NIRS need to be considered. First, NIRS measures the blood oxygenation changes within the illuminated area, which includes both intracranial and extracranial tissues [33]. NIRS parameter changes could, therefore, be elicited by changes in blood flow

Table 1
Mean ± S.D. laterality ratio scores of Oxy-Hb and Total-Hb in two subject groups separated by heart rate variation

	HR variation	Ratio of Oxy-Hb	Ratio of Total-Hb
Higher HR Group ($N = 8$)	14.24 ± 2.99	0.17 ± 0.11	0.17 ± 0.17
Lower HR Group ($N = 8$)	3.64 ± 2.83	−0.28 ± 0.21	−0.35 ± 0.24
t-test	$P < 0.00001$	$P < 0.001$	$P < 0.001$

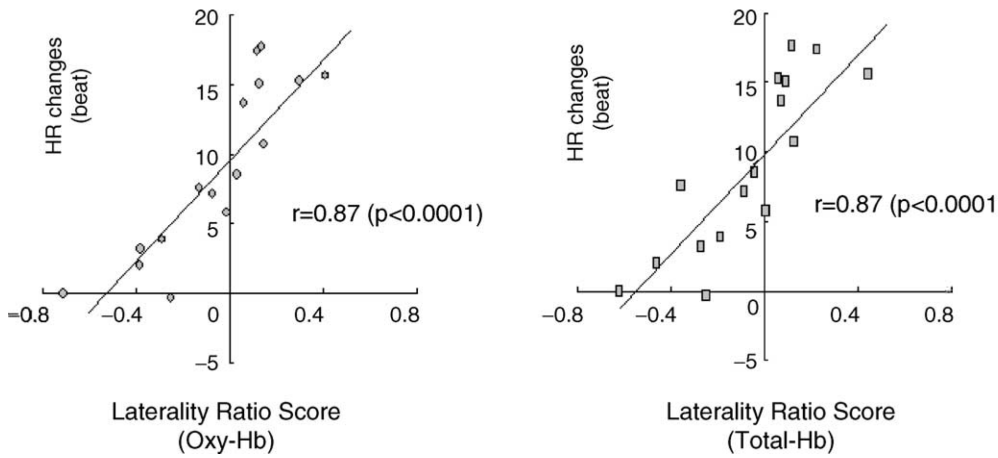

Fig. 2. Relationship between the laterality ratio scores and heart rate (HR) changes. The vertical and horizontal axes denote change in HR (beat) and the laterality ratio scores (Oxy-Hb and Total-Hb), respectively. Significant positive correlations were observed in both Oxy-Hb (r = +0.87, $P < 0.0001$) and Total-Hb (r = +0.85, $P < 0.0001$).

of the scalp; however, the changes induced by neuronal activation are believed to reflect the changes in CBO and hemodynamics within the activated cortices [12,13,15–17,28,29]. Second, NIRS reflects the average changes of CBO within the illuminated area; thus, the evoked-CBO changes in the present study indicate the average CBO changes in that part of the prefrontal cortex through which the near infrared light passes. Finally, continuous wave NIRS such as NIRO-300 does not yield absolute values for the hemoglobin concentration changes without information concerning the optical pathlength in each subject [5]. However, we did not find any significant differences in optical pathlength between the right and left frontal regions of five subjects. Zhao et al. [38] reported that the optical pathlength was relatively homogeneous in the forehead as compared to the other regions of the head such as the frontal-temporal junction. These observations support the feasibility of the data analysis undertaken in the present study.

The MA task caused increases of Oxy-Hb and Total-Hb associated with a decrease of Deoxy-Hb in the right and left prefrontal cortices of all subjects. These NIRS parameter changes indicate activation within the prefrontal cortex [12,13,15–17,28,29]. The increases of Oxy-Hb and Total-Hb reflect the occurrence of rCBF increases in response to neuronal activation, and the decrease of Deoxy-Hb is caused by evoked-rCBF rises which exceed the increases in O_2 consumption during neuronal activity [7]. Several fMRI studies have demonstrated activation in the prefrontal cortex during MA tasks [10,19,22]. In addition, MA tasks cause activation within several brain regions such as the parietal cortex. Gruber et al. [10] found that the prefrontal and parietal cortices were activated during both MA and non-mathematical tasks, and they suggested that these regions support more general cognitive operations rather than specific modules for calculation. The prefrontal cortex activity occurring during the MA task in the present study might, therefore, reflect general cognitive operations such as attention and emotion.

We found that, in the high-HR group, the laterality ratio scores for Oxy-Hb and Total-Hb showed positive values, while in the low-HR group, the laterality ratio scores showed negative values. In addition, a significant positive correlation between HR and the laterality ratio score for Oxy-Hb indicated that higher right prefrontal activity than left during the MA task was associated with increases in HR. In view of the strong correlation between evoked-CBF changes and field potentials [21], the present data suggest that the activity in the right prefrontal cortex was greater than that in the left prefrontal cortex in the subjects with greater HR increases. Anatomical studies have demonstrated direct projections from the prefrontal cortex to the brain stem and spinal regions involved in cardiovascular control [34]. The right-sided innervations of the vagus nerve and sympathetic fibers exert a greater influence on the sinoatrial node than do the left-sided innervations, leading to a greater influence on HR. Based on these observations, we infer that the right prefrontal cortex activity during the MA task may modulate HR by virtue of increasing sympathetic effects or decreasing parasympathetic effects via neural networks between the prefrontal cortex and the subcortical structures.

The present findings are consistent with the reported cerebral asymmetry in regulations of the ANS. Data obtained by electrical stimulation of the cortex, unilateral hemispheric inactivation and selective sensory stimulation have suggested that the left hemisphere predominantly modulates parasympathetic effects while the right hemisphere predominantly modulates sympathetic effects of the ANS [25,36,37]. However, Ahern et al. [1] re-investigated this issue by performing intracarotid amobarbital administration in a large number of subjects, and concluded that the right hemisphere plays a greater role in the cerebral regulation of cardiac function by virtue of the modification of parasympathetic effects. The cerebral asymmetry of ANS regulation thus still remains in dispute.

In addition, the frontal cortex activities during mental stress and their relation to the ANS are still controversial. For example, employing single-photon emission computed tomography (SPECT), Shapiro et al. [31] observed a decrease of rCBF in the prefrontal cortex during the MA task associated with an increase of HR; the rCBF reduction was greater in the high hostility subjects. The following explanations for such disparities deserve consideration. First, difference in techniques for evaluating the activation need to be taken into account. NIRS measures CBO changes in part of the prefrontal cortex, while SPECT can obtain tomographic images of rCBF changes over the whole prefrontal cortex. NIRS might, therefore, overlook areas associated with a decreased rCBF. Second, individual differences in basal conditions can affect the results. In activation studies, which employ neuroimaging techniques such as SPECT, the levels of rCBF at rest affect the evoked changes in rCBF. When the rCBF was high at rest, the rCBF could be decreased during tasks (i.e., deactivation) [26]. This may explain why the above high hostility subjects showed a greater reduction of their rCBF during the MA task [31], if the resting rCBF was higher in the subjects with high hostility than those with low hostility. Third, the degree of experienced stress could account for heterogeneity of the results. PET studies on simple phobics' fear have indicated that more severe stress rather decreases than increases activity in the prefrontal cortex [8]. Finally, it should be noted that all of the subjects in the present study were female. Several functional brain imaging studies have demonstrated gender-differences in regional brain activity during different cognitive and emotional tasks [11]. The present results could, therefore, differ from results obtained in males and should not be generalized to the male population.

In summary, the present data indicate that the MA task-induced activity in the right prefrontal cortex was larger than that in the left prefrontal cortex in subjects with greater HR increases. These findings support the hypothesis that right prefrontal cortex activity predominantly modulates sympathetic effects during the MA task.

Acknowledgment

This work was supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Sciences and Technology of Japan (a grant for the promotion of industry-university collaboration at Nihon University) and by Hamamatsu Photonics K.K. (Hamamatsu, Japan).

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