Brain Stimulation 12 (2019) 778–780

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Time courses of BOLD responses during transcranial near-infrared laser irradiation

Dear Editor:

We have reported the results of blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) during near infrared (NIR) laser irradiation in five healthy volunteers [1]. Since August 2008, after approval of institutional review board of National Defense Medical College, the appropriate informed consent was obtained, and the transcranial NIR light emitting diodes (LED) treatments were initiated for the patient presented with dementia associated with hypofrontality [2]. Hypofrontality is a state of decreased cerebral blood flow (CBF) in the prefrontal cortex. Here we present a case of multi-infarct dementia showed conspicuous BOLD responses during near infrared (NIR) laser irradiation. The patient was 77 years old male. He presented with memory disturbance, aphasia and decreased spontaneity. Head MRI showed multiple lacunae in the bilateral basal ganglia and a cortical infarct in the left temporo-parietal region. CBF measurements before NIR LED treatment indicated hypofrontality. NIR LED treatment consists of 28 days from an array of 23 × 850nm LEDs, 13 mW each, 15 mins per session, the power density 11.4 mW/cm2 at the forehead [2]. He showed increased spontaneity and improvement in speech fluency following NIR LED treatment. After NIR LED treatment, we have performed BOLD fMRI in a resting state during near infrared laser irradiation in this patient. The time course of BOLD signals was also extracted. Fig. 1 An indicates a time table of pretreatment (15 min) by NIR LED, subsequent fMRI during 30 mW/cm^2 NIR irradiation (9 min), and 200 mW/cm^2 NIR irradiation (9 min). A photograph of a model being treated, L-light (SUN-MECHATRONICS, Tokyo) and photographs of a MRI gantry captured by NIR CCD camera during NIR irradiation.

Immediately after a 15 minutes of NIR LED treatment (Fig. 1 A left), at a power density of 30 (Fig. 1 A middle), and 200 mW/cm^2 (Fig. 1 A right) functional images were acquired using T2*-weighted gradient echo planar imaging sequence (repetition time = 3000 ms, echo time = 35 ms, flip angle = 90°, matrix size = 96 × 96 (ZIP 128), 4.5 mm slice thickness with no interslice gap, and one excitation) covering the entire brain. Block design fMRI was done. Data acquisition was performed through 3 cycles of 90 seconds irradiation and 60 seconds rest periods as reported previously [1]. Neuronal activation maps were color-coded according to the statistical significance of difference between the rest and irradiation states and overlaid over the anatomical T1-weighted images for anatomical reference. We chose a t-value threshold of 3.5. T-statistics were derived from the resulting correlation coefficients, with threshold for activation set at $t < 3.5$ ($P < 0.001$, uncorrected). The result of this procedure was to identify the set of voxels that showed significant activation to the NIR irradiation. Immediately after a 15 minutes of NIR LED treatment, striking BOLD responses were observed at a power density of 30 mW/cm^2 in the dosolateral prefrontal cortex just beneath the fiber optics (green arrow and green line) (Fig. 1 B) and widespread areas of the whole brain including the ipsilateral parietal cortex (purple arrow and purple line) (Fig. 1 B) and the contralateral caudate nucleus (blue arrow and blue line) (Fig. 1 B). The time course of BOLD signals at these areas are synchronously and exactly matched (Fig. 1 B). The increase in BOLD signals did not at all consist of a single rise and fall [3]. Significant BOLD responses were also observed at a power density of 30 mW/cm^2 in the brain areas including the bilateral occipital cortices (blue and purple arrows and blue and purple lines) (Fig. 1 C) and the contralateral temporal cortex (green arrow and green line) (Fig. 1 C). The time course of BOLD signals at these areas are not synchronously matched (Fig. 1 C). Subsequently, 9 min after cessation of a 15 minutes of NIR LED treatment, a restricted BOLD response was observed at a power density of 200 mW/cm^2 in the dosolateral prefrontal cortex just beneath the fiber optics. However, BOLD responses in the widespread areas of the whole brain was no more observed (Fig. 1 D). In the pathological condition such as cerebral ischemia, alteration in cytochrome *c* oxidase activity and alteration in its redox state is well documented [4,5]. Cytochrome *c* oxidase is a major photoacceptor for NIR light. The threshold of BOLD responses during near infrared (NIR) laser irradiation may be altered in pathological conditions. It is unclear exactly what threshold of power density in mW/cm^2 is required in the brain to have a biological effect [6]. Nitric oxide from the irradiated scalp may affect the brain. Widespread increase of BOLD responses following a 15 minutes of NIR LED treatment could be attributed to the increased blood nitric oxide concentration [7]. It is noteworthy that the time course of BOLD signals at the right dorsolateral prefrontal cortex, the ipsilateral parietal cortex and the contralateral caudate nucleus are synchronously matched in this case. The time course of BOLD responses may help reveal the neuronal network in human brains [8]. Prefrontal corticostriatal afferents to the caudate nucleus have been implicated in motor and cognitive functions [9]. We hope NIR induced BOLD fMRI will promote clinical studies investigating the efficacy of NIR treatment.

https://doi.org/10.1016/j.brs.2019.01.006

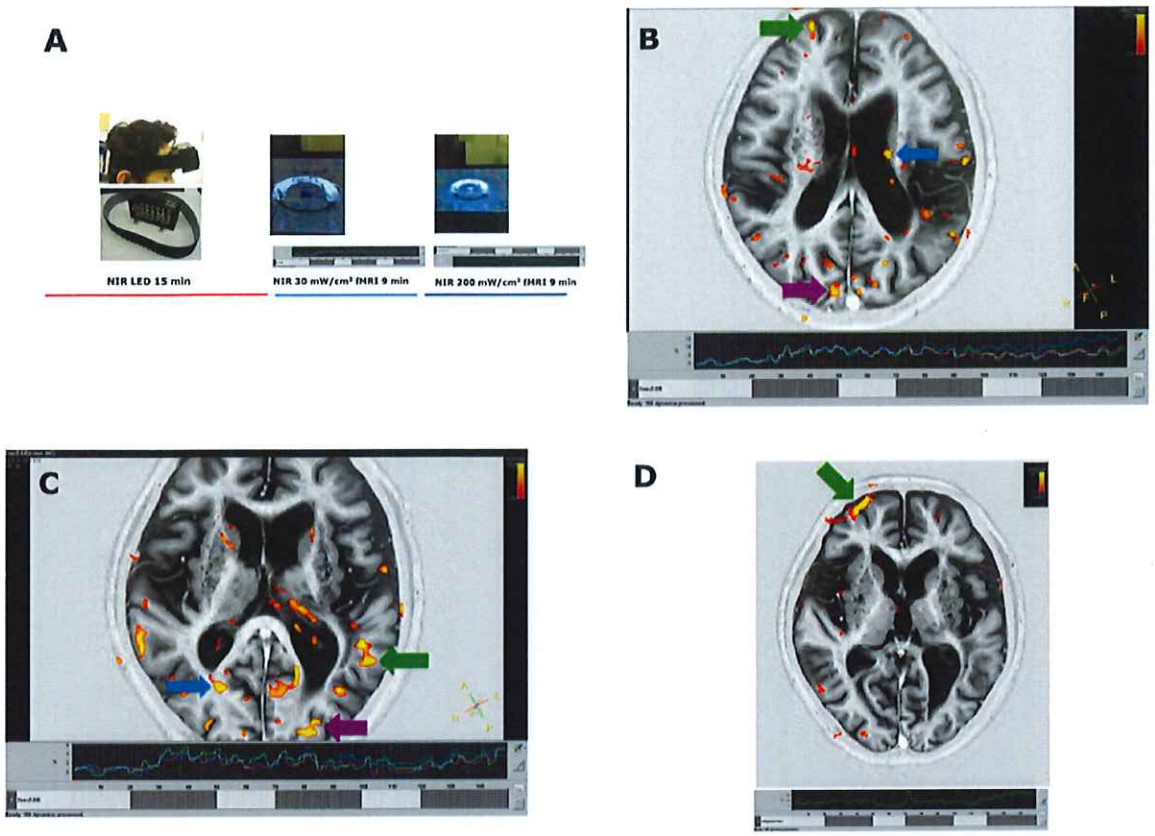

Fig. 1. **A:** A time table of pretreatment (15 min) by NIR LED, subsequent fMRI during 30 mW/cm^2 NIR irradiation (9 min), and 200 mW/cm^2 NIR irradiation (9 min). A photograph of a model being treated, L-light (SUN-MECHATRONICS, Tokyo) and photographs of a MRI gantry captured by NIR CCD camera during NIR irradiation.
B: Immediately after a 15 minutes of NIR LED treatment, significant BOLD responses was observed at a power density of 30 mW/cm^2 in the dosolateral prefrontal cortex just beneath the fiber optics (green arrow and green line) (Fig. 1 B) and widespread areas of the whole brain including the ipsilateral parietal cortex (purple arrow and purple line) (Fig. 1 B) and the contralateral caudate nucleus (blue arrow and blue line) (Fig. 1 B). The time course of BOLD signals at these areas are synchronously and exactly matched (Fig. 1 B). The increase in BOLD signals did not at all consist of a single rise and fall.
C: Immediately after a 15 minutes of NIR LED treatment, significant BOLD responses was observed at a power density of 30 mW/cm^2 in the brain areas including the bilateral occipital cortices (blue and purple arrows and blue and purple lines) (Fig. 1 C) and the contralateral temporal cortex (green arrow and green line) (Fig. 1 C). The time course of BOLD signals at these areas are not synchronously matched (Fig. 1 C).
D: Nine minutes after cessation of a 15 minutes of NIR LED treatment, a restricted BOLD response was observed at a power density of 200 mW/cm^2 in the dosolateral prefrontal cortex just beneath the fiber optics (green arrow and green line) (Fig. 1 D). However, BOLD responses in the widespread areas of the whole brain was no more observed (Fig. 1 D).
(For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Conflicts of interest

We, all authors certify that there is no conflict of interest.

This study was supported partly by a research grant from The General Insurance Association of Japan. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgements

We appreciate the help from Radiology department of Tokorozawa Central Hospital for functional MRI data acquisition.

References

[1] Nawashiro H, Sato S, Kawauchi S, Takeuchi S, Nagatani K, Yoshihara N, et al. Blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) during transcranial near-infrared laser irradiation. Brain Stimul 2017;10:1136–8.
[2] Nawashiro H, Wada K, Nakai K, Sato S. Focal increase in cerebral blood flow after treatment with near-infrared light to the forehead in a patient in a persistent vegetative state. Photomed Laser Surg 2012;30:231–3.
[3] Ibinson JW, Vogt KM. Pain does not follow the boxcar model: temporal dynamics of the BOLD FMRI signal during constant current painful electric nerve stimulation. J Pain 2013;14:1611–9.
[4] Kawauchi S, Sato S, Ooigawa H, Nawashiro H, Ishihara M, Kikuchi M. Simultaneous measurement of changes in light absorption due to the reduction of cytochrome c oxidase and light scattering in rat brains during loss of tissue viability. Appl Opt 2008;47:4164–76.
[5] Sanderson TH, Wider JM, Lee I, Reynolds CA, Liu J, Lepore B, et al. Inhibitory modulation of cytochrome c oxidase activity with specific near-infrared light wavelengths attenuates brain ischemia/reperfusion injury. Sci Rep 2018;8:3481.
[6] Hamblin MR. Shining light on the head: photobiomodulation for brain disorders. BBA Clin 2016;6:113–24.
[7] Mitchell UH, Mack GL. Low-level laser treatment with near-infrared light increases venous nitric oxide levels acutely: a single-blind, randomized clinical trial of efficacy. Am J Phys Med Rehabil 2013;92:151–6.
[8] d'Avossa G, Shulman GL, Corbetta M. Identification of cerebral networks by classification of the shape of BOLD responses. J Neurophysiol 2003;90:360–71.
[9] Wang H, Pickel VM. Dendritic spines containing mu-opioid receptors in rat striatal patches receive asymmetric synapses from prefrontal corticostriatal afferents. J Comp Neurol 1998;396:223–37.

Hiroshi Nawashiro*, Satoko Kawauchi, Yasuyuki Tsunoi, Shunichi Sato
Division of Bioinformation and Therapeutic Systems, National Defense Medical College Research Institute, Tokorozawa, Saitama, Japan

E-mail addresses: hiroshinawashiro@yahoo.co.jp (H. Nawashiro), skawauch@ndmc.ac.jp (S. Kawauchi), ytsunoi@ndmc.ac.jp (Y. Tsunoi), ssato-bits@ndmc.ac.jp (S. Sato).

9 December 2018

* Corresponding author. Division of Neurosurgery, Tokorozawa Central Hospital, 3-18-1 Kusunokidai, Tokorozawa, Saitama 359-0037, Japan.

Available online 16 January 2019