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Principle and technique of NIRS-Imaging for human brain FORCE: fast-oxygen response in capillary event

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Abstract. Two basic principles to measure positional information using photon have been discovered. The first one is the photon-CT (pCT) technique using straight-line light by Jobsis in 1977. The second is NIRS-Imaging of diffusion/scattering light that was discovered in 1991 by Kato. In the principle of NIRS-Imaging, a position of two probes and temporal responses of a measuring object determines each photon's functional pixels with border unclearness. As NIRS-Imaging uses uncertain light of positional information, it is thought of as a reversal to locate spatial information. At this point, for the pCT, which depends on precision of light for positional information, NIRS-Imaging is a completely opposite principle. It is difficult to penetrate the adult brain with light by pCT. With the discovery of the principle of NIRS-Imaging, which samples photon functional pixels, local blood physiology for oxygen exchange rapidly developed in brain and muscle studies. The sensibility of NIRS-Imaging is high for a signal of active oxygen exchange in capillaries. NIRS-Imaging is a non-invasive measurement for cerebral microcirculation in the capillary, not the vein. It is important to measure fast-oxygen response in capillary event (FORCE) related to neuronal responses, defined as the FORCE effect. Advanced NIRS-Imaging can distinguish the FORCE effect from a watering-the-garden effect. The slow blood change that defined a watering-the-garden effect can induce a strong signal in the vein by PET and fMRI. Therefore, oxygen consumption in tissues using fMRI and PET may be underestimated by the measurement of the passive washout flow in the vein. © 2004 Published by Elsevier B.V.

Keywords: Near-infrared spectroscopy (NIRS)-Imaging; Oxygen; Fast-oxygen response in capillary event (FORCE); Watering-the-garden effect; Photon functional pixel (PFP)

1. Introduction

Novelty in science is produced by access to the basic principle. Birth of a basic principle for functional imaging using light was similar too. Since 1977 the principle of NIRS-Imaging has acted as an antithesis to photon-CT (pCT). pCT uses straight-line light

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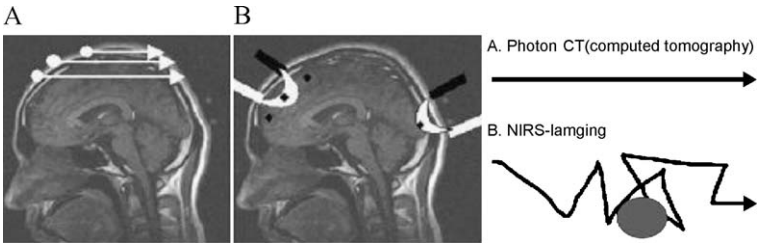


Fig. 1. Two basic principles to measure positional information, which used light. (A) Photon-CT of straight-line light by Jobsis in 1977. (B) NIRS-Imaging of diffusion/scattering light discovered in 1991 by Kato.

[1] (Fig. 1A). NIRS-Imaging by Kato and coworkers uses diffusion/scattering light [2,3] (Fig. 1B). Furthermore, Kato studied a principle of NIRS-Imaging more deeply. In the principle of NIRS-Imaging, a photon functional pixel (PFP) with border unclearness is decided by a position of two probes and local temporal responses of a measuring object. As NIRS-Imaging uses uncertain light of positional information, it is thought to be a reversal to locate spatial information. At this point, for the pCT, which depends on precision of light for positional information, NIRS-Imaging is a completely opposite principle. By discovery of a principle and the technique of NIRS-Imaging, which samples PFP, NIRS-Imaging was rapidly developed to measure local, temporal–spatial function from brain oxygenation monitoring. The physiological meaning of the changes in oxygenated hemoglobin (HbO_2) and deoxygenated hemoglobin (HbR) completely changed into local temporal–spatial information by this discovery.

2. Discovery of NIRS-Imaging

NIRS-Imaging, whereby near infrared rays (700–1300 nm, Fig. 2A) are irradiated from the skin of the head through the skull into the brain to measure changes of HbO_2 and HbR in the microvessel of the cortex, has progressed rapidly. NIRS-Imaging has the advantages that metabolism of separate tissue can be measured non-invasively and that this can furthermore be implemented with a simple apparatus (portability), unlike PET and fMRI. Using bedside NIRS-Imaging, it was possible to observe cerebral activity in a child and even a bedridden old person. It is the setting of a distance of 2.5 cm between

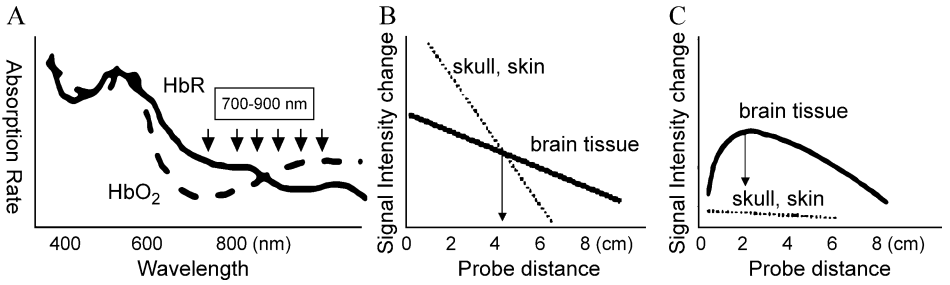


Fig. 2. The concept of NIRS-Imaging for shortening probe distance. (A) Absorption rates of HbO_2 and HbR. A qualitative simulation of light penetration into a brain during a resting state (B) and during an active state (C).

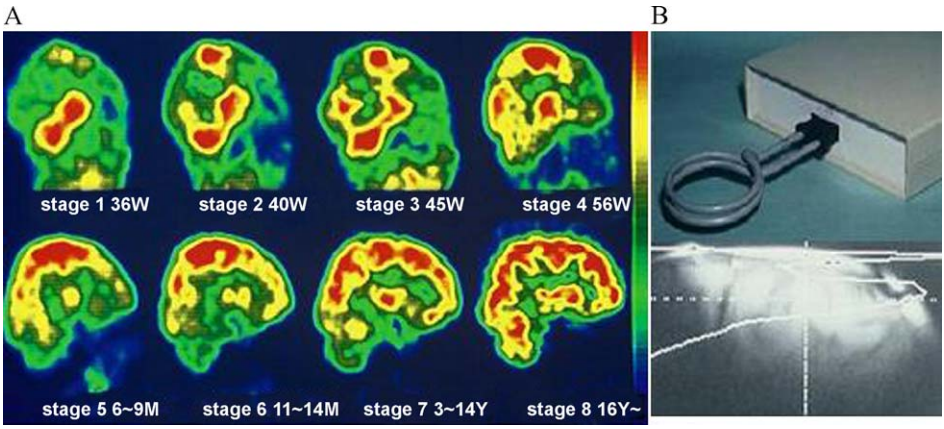


Fig. 3. The concept of NIRS-Imaging of multiple surface probes for brain surface mapping. Differing cerebral blood flow distribution from neonates to adults [4]. (B) Surface coil for MR spectroscopy and brain surface imaging by surface coil [5].

probes that symbolized the birth of NIRS-Imaging. As the distance from the skull surface to the cortex is 1.5–2 cm, it was necessary to separate the distance of the probes more than 4.25 cm for sampling brain tissue during the resting state (Fig. 2B). Therefore, it is not exaggeration to say that the basic principle of NIRS-Imaging is a new technique, which can shorten the probe distance of 4.25 cm. Kato et al. found that they could shorten the distance of the probes to approximately 2.5 cm if they used a local cerebral response (Fig. 2C). In fact, Kato et al. conducted photo-stimulus experiments in humans in which near infrared light was irradiated to parts of the brain. As a result, they showed that it was able to monitor the distribution of localized brain function at the bedside and proved low resolution optical imaging using this bedside method of non-invasive detection of local brain function.

As for the pCT, measurement takes time. Even if we are going to use brain oxygen monitoring in neonates, it is weak for motion artifacts. In addition, Kato's 1988 thesis of brain development in neonates understood that a development pattern of cerebral blood flow distribution was associated with cerebral myelination, such as that shown in Fig. 3A [4]. Thus, we hypothesized that a cerebral oxygen state of neonates depended on the probe location for different cerebral blood flow distribution. MR spectroscopy using a surface coil is a non-invasive measurement of local cerebral metabolism for a functional pixel with border unclearness (Fig. 3B). Kato came up with the idea of NIRS-Imaging of multiple surface probes for brain surface mapping.

3. Fast-oxygen response in capillary event (FORCE)

As PFP with border unclearness is decided by the position of two probes and temporal responses of a measuring object using NIRS-Imaging, it is very important to understand the different physiological responses between resting and active states in the capillary and vein (Fig. 4). Signal increases in T2*-fMRI are believed to result from decreased paramagnetic HbR in the activation area. This mechanism has been described widely as

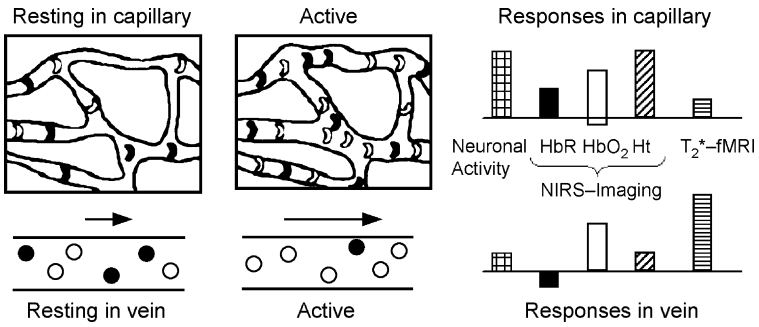


Fig. 4. Functional physiology in capillaries and veins using NIRS-Imaging and T2*-fMRI.

the blood oxygenation level dependent (BOLD) theory (Fig. 5A). The signal changes of T2*-fMRI may be paralleled with HbR by passive washout flow in the large vein. However, by oxygen exchange in the capillary, a simple washout flow hardly occurs in an active location. Therefore, the non-BOLD effect does not change in parallel with HbR in the capillary and micro-vein. A non-BOLD effect, which indicated discrepancies in this canonical BOLD theory, has been found in studies using optical techniques that directly measure hemoglobin changes (Fig. 5B) [6,8]. To understand different sensitivities between NIRS-Imaging and T2*-fMRI, the hematocrit (Ht) must be taken into account. In the blood in veins between resting and active states, there is less variation of hematocrit in comparison to the blood in capillaries [6]. The signal change in the vein is always larger than in the capillary when using T2*-fMRI [6–8]. In contrast, the signal change in the capillary is always larger than in the vein when using NIRS-Imaging. It is very difficult to detect a signal from the vein by using light for strong absorption.

The T2*-fMRI is sensitive to passive hemodynamic changes in a vein area where blood flow from both activated and non-activated areas is mixed, such as in the secondary watering-the-garden effect (a phenomenon of scattering water on a circumference in order to give water to one flower), but is less sensitive to active hemodynamic changes in a capillary area of an activation focus, such as the FORCE effect. Hemodynamics in capillaries differs greatly from that in veins. In veins, blood flow changes with a mild increase in blood volume and a constant hematocrit. In activation capillaries, the number of red

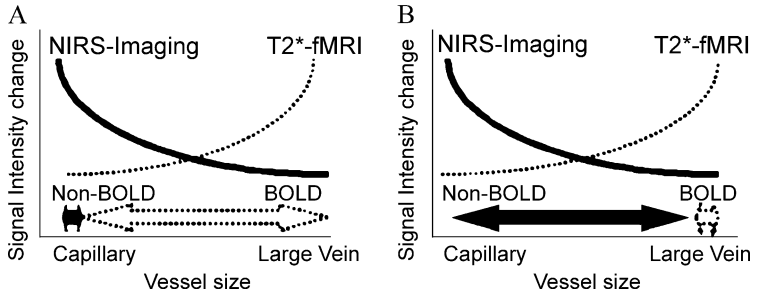


Fig. 5. Sensibility of NIRS-Imaging and T2*-fMRI for blood response in capillaries and veins. (A) Canonical BOLD hypothesis from blood physics; (B) hemodynamic bridging theory from blood physiology [6].

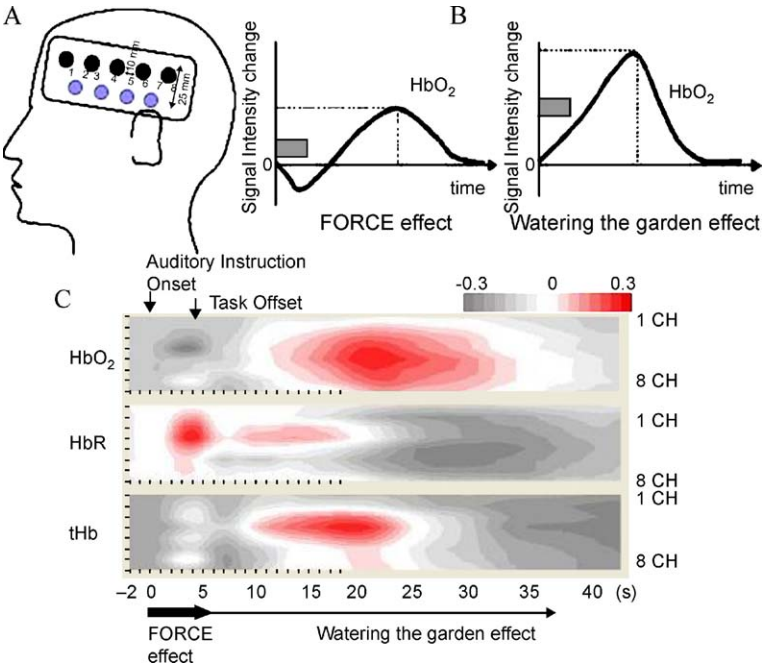
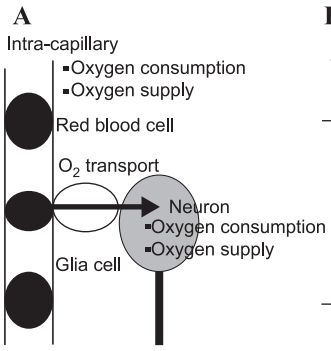


Fig. 6. Imaging for oxygen exchange in the capillary: distinguished FORCE effect from watering-the-garden effect. (A) The location of eight channels for NIRS-Imaging. The probes were placed on bilaterally front-temporal regions covered Broca's area. Sampling rate of data acquisition was 10 Hz. (B) The dynamic changes of HbO_2 in FORCE effect and watering-the-garden effect. The maximum peak of HbO_2 in FORCE effect was delayed and lower in comparison to watering-the-garden effect. (C) Temporal spatial mapping during a language task. An instructor speaks a word directly and exhibits it. Subject repeats immediately thereafter [9].

blood cells increases greatly with an increase in hematocrit. Therefore, the FORCE effect, measured by NIRS-imaging, is a good marker to observe the activation focus in comparison to secondary watering-the-garden effect (Fig. 6).



B

Response order	Physiology	Location	Effective sampling
1st	Neuronal response	tissue	EEG, MEG
2nd	Oxygen exchange,consumption (FORCE effect)	in capillary	NIRS-Imaging
3rd	Active oxygen supply (1st watering-the-garden effect)	in capillary	NIRS-Imaging, PET
4th	Passive washout flow (2nd watering-the-garden effect)	in vein	fMRI, PET

Fig. 7. A schema of oxygen exchange and supply in capillaries and neurons (A) and sensitivity of modalities for functional response (B).

4. Tight linkage between FORCE and neuronal activity

Advanced NIRS-Imaging could distinguish the FORCE effect from a watering-the-garden effect during early language action. As blood responses were diffuse and broad, it is important to measure the FORCE effect related to neuronal response as a 2nd order response (Fig. 7A). The secondary watering-the-garden effect as a 4th-order response causes a big signal change in T2*-fMRI and PET studies (Fig. 7B). Our finding supported the technical insensibility in T2*-fMRI for the first 3–5 s [10] due to the non-BOLD effect in the capillary. Neuroimaging, using PET and MRI, should pay attention to the physiological misunderstanding and underestimation of oxygen consumption [11] due to the technical insensibility of the FORCE effect from NIRS-Imaging. NIRS-Imaging is a non-invasive measurement for cerebral microcirculation in the capillary, not in the vein. We need to understand further the relationship between FORCE and neuronal activity.

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