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Illuminating the Black Box: Investigating Prefrontal Cortical Hemodynamics During Exercise With Near-Infrared Spectroscopy

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Near-infrared spectroscopy (NIRS) presents an appealing option for investigating hemodynamic changes in the cerebral cortex during exercise. This review examines the physical basis of NIRS and the types of available instruments. Emphasis is placed on the physiological interpretation of NIRS signals. Theories from affective neuroscience and exercise psychobiology, including Davidson's prefrontal asymmetry hypothesis, Dietrich's transient hypofrontality hypothesis, and Ekkekakis's dual-mode model, are reviewed, highlighting the potential for designing NIRS-based tests in the context of exercise. Findings from 28 studies involving acute bouts of exercise are summarized. These studies suggest that the oxygenation of the prefrontal cortex increases during mild-to-moderate exercise and decreases during strenuous exercise, possibly proximally to the respiratory compensation threshold. Future studies designed to test hypotheses informed by psychological theories should help elucidate the significance of these changes for such important concepts as cognition, affect, exertion, and central fatigue.

Keywords: near-infrared spectroscopy, prefrontal asymmetry, exercise intensity, affective responses

One of the benefits of neuroscience for psychology, according to Peter Lang (1994), is that it can help "limit inference and . . . keep our cognitive theories away from empty boxology" (p. 219). In other words, neuroscientific knowledge can steer psychological theorizing in the right direction (and away from the wrong direction) by suggesting what is possible (and what is impossible) at the level of the nervous system. For example, is "mind over muscle" true? Some may believe so. In fact, some have argued so. But is this really possible? Does the central nervous system have the necessary anatomical features and neurophysiological functions that would permit, for example, consciousness to become completely impervious to afferent muscular cues or volition to exert unlimited control over muscular contractions? Having an understanding of what the brain "does" during exercise could help reformulate, refine, or place important boundary conditions on these and numerous other theoretical propositions.

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Unfortunately, the progress made by exercise neuroscience has been slow (Dishman, 2005). In particular, knowledge of what happens in the brain *during* a bout of exercise remains sketchy. A relatively small number of animal studies have provided insights into areas implicated in cardiovascular and locomotor control. However, most psychologists would probably be more interested in the function of the frontal lobes, where animal-to-human inferences are limited or impossible, given the dramatic interspecies differences in that particular region. In psychological research, the puzzle of the function of the various subdivisions of the frontal cortex is systematically and painstakingly being solved using the imaging tools of modern human neuroscience. For example, great strides are being made in understanding the role of the frontal cortex in various types of cognitive operations (Alvarez & Emory, 2006; Nee, Wager, & Jonides, 2007) and in the cognitive control of emotions (Ochsner & Gross, 2005, 2007; Phan, Wager, Taylor, & Liberzon, 2002) and pain (Apkarian, Bushnell, Treede, & Zubieta, 2005). However, for research focusing on cortical function *during exercise*, various obstacles (e.g., susceptibility to movement-related artifact, high cost, or invasive nature) have precluded the widespread use of neuroimaging methods and have thus limited the knowledge that has been obtained.

For example, electroencephalography (EEG), particularly in conjunction with sophisticated source localization procedures, given its noninvasive nature, excellent temporal resolution, and relatively low cost, could be informative. However, only a handful of studies have reported EEG results during exercise (see review by Crabbe & Dishman, 2004). None of them involved a high-density electrode array (to improve spatial resolution) or source localization procedures (to provide some indication of the possible sources, within the brain, of the signals detected at the surface of the skull). Presumably the most serious drawback, which can explain this dearth of data, is that the chances of obtaining meaningful, "clean" data during exercise of any intensity, but particularly during exercise of high intensity, are slim because of the rather extreme susceptibility of this method to movement and muscular artifacts (Petruzzello, Ekkekakis, & Hall, 2006; Thompson, Steffert, Ros, Leach, & Gruzelier, 2008). The high susceptibility to similar types of artifact and the high cost have also limited the use of magnetoencephalography (MEG) for investigating brain activity during acute exercise (Lewis, 2003).

Single-photon-emission computed tomography (SPECT) is an imaging technique used to examine changes in regional cerebral blood flow and, more recently, neurotransmitter kinetics. This technique offers the significant advantage that the brain scanning can be performed *after* the behavior or task of interest and still reflect brain activity *during* that behavior or task. This is accomplished by the intravenous injection or inhalation (during the task being investigated) of a radioactive tracer that is quickly taken up by activated brain cells and then "trapped" there for a period of time (up to several hours, depending on the tracer). This allows the task (e.g., a bout of exercise) to be completed in ecologically valid conditions (even in the field). The scanning can be performed at a later time but would still reflect neuronal activity at the time of the injection. Participants can remain motionless during the actual scanning and thus movement-related artifact does not present a problem. Given this flexibility, SPECT has been used to examine the activity of certain brain regions during exercise (Williamson, 2006). On

the other hand, the use of injections and radioactive tracers makes this technique invasive and most potential participants are reluctant to volunteer. Furthermore, its temporal resolution is poor because brain activity reflected in SPECT images represents a period of neuronal uptake extending from a few seconds to a few minutes following the introduction of the tracer. Finally, the cost of instrumentation is high and made even higher by the fact that, to permit meaningful interpretation, SPECT images (like those obtained from MEG, which was mentioned earlier, and positron-emission tomography, which is described next) must be coregistered with high-resolution anatomical images, necessitating additional access to a magnetic resonance scanner.

Positron-emission tomography (PET) also involves the injection of radioactive tracers, albeit of lower atomic weights and shorter half-lives than those used for SPECT. Used in combination with different tracers, PET can be used to study several important parameters of neuronal activity, including regional cerebral blood flow, glucose metabolic rate, and receptor density and affinity, typically with higher image resolution than obtained with SPECT. On the other hand, owing to the short half-lives or rapid washout of most tracers, PET scanning must begin immediately after the injection of the tracers. In practical terms, this means that, for the study of most parameters, the participants must lay motionless in the scanner while performing the behavior or task of interest (precluding studies of acute exercise) or experimental protocols must be limited to the study of changes from one scanning session before to another scanning session after the behavior of interest, such as an exercise bout (Boecker et al., 2008). An exception is the study of glucose metabolic rate using [^{18}F]fluoro-deoxy-glucose (FDG). This radioactive analog of glucose has a relatively long half-life (110 min) and, like the heavier isotopes used in SPECT, is "trapped" within metabolically active cells, permitting PET scanning 30–60 min after the injection. Because of this property, [^{18}F] FDG-PET has been used in several studies for the examination of brain activity *during* bouts of exercise (Tashiro, Itoh, Fujimoto, Masud, Watanuki, & Yanai, 2008). However, because PET measurements reflect the uptake of tracers over a period of several seconds or minutes, the temporal resolution of the method is poor. Moreover, the cost of PET is even higher than that of SPECT and is further inflated by the need for a nearby cyclotron (a type of particle accelerator), an expensive device needed for the production of fresh isotopes. Finally, as was the case with SPECT, the injection of radioactive tracers renders PET unappealing to most potential participants.

Functional magnetic resonance imaging (fMRI) is now widely accepted as the neuroimaging gold standard as a result of a compromise between temporal and spatial resolution, combined with it being a relatively noninvasive procedure (i.e., not requiring the injection of tracers but requiring the placement of the participant in a confined and noisy space). Nevertheless, the high cost of instrumentation has restricted the application of the technique to only the most highly funded research institutions, while its susceptibility to movement artifact continues to present considerable challenges for the investigation of brain responses during exercise (Mehta, Verber, Wieser, Schmit, & Schindler-Ivens, 2009).

Near-infrared spectroscopy (NIRS; Hoshi, 2003, 2005; Madsen & Secher, 1999; Owen-Reece, Smith, Elwell, & Goldstone, 1999; Rolfe, 2000; Villringer & Chance, 1997; Villringer & Obrig, 2002) is a technique that permits the investiga-

tion of oxygenation patterns in most biological tissues, including the cerebral cortex. Compared with the other neuroimaging methods outlined earlier, NIRS has both some important strengths and some notable limitations. On the one hand, the advantages of the technique include good temporal resolution (adequate to investigate relatively slow hemodynamic changes and even adequate to investigate millisecond-range neural signals), noninvasive measurement procedures, relatively low cost, lack of interference from electromagnetic radiation, and, importantly for exercise scientists, an acceptable signal-to-noise ratio during exercise. On the other hand, unless a multichannel system is used (raising the cost to fairly high levels), NIRS does not have good spatial resolution (Boas, Dale, & Franceschini, 2004; Strangman, Boas, & Sutton, 2002). Furthermore, depth coverage is not good, so most NIRS investigations are limited to relatively superficial layers of tissue. In the case of the brain, this means that subcortical structures are beyond the reach of current NIRS methods (Gratton, Fabiani, Elbert, & Rockstroh, 2003). Nevertheless, it could be argued that, for researchers interested in investigating cortical activity *during* exercise bouts, NIRS offers the most realistic option that is currently available.

The purposes of this review are the following: (a) to introduce the basic operational principles of NIRS in terms that can be understood by nonspecialists, (b) to describe the different types of NIRS instruments that are available commercially, (b) to explain the physiological significance of NIRS signals and their compatibility with the blood-oxygenation-level-dependent (BOLD) signal of fMRI, (c) to summarize three theoretical models that could be tested with NIRS in the context of exercise (Davidson's prefrontal asymmetry hypothesis, Dietrich's transient hypofrontality hypothesis, and Ekkekakis's dual-mode model), (d) to review the findings of the first 28 studies in which NIRS has been used to investigate cortical hemodynamics during acute bouts of exercise, and (e) to propose a tentative framework for the interpretation of hemodynamic changes in the prefrontal cortex during exercise.

NIRS: Basic Principles

NIRS uses light in the near-infrared spectrum to investigate specific properties of biological tissues. The near-infrared light spectrum ranges from a wavelength of 700 nm to 1400 nm. Above 900 nm, water absorbs nearly all photons within only a few millimeters in normally hydrated tissues, not allowing much light to pass through. Below 700 nm, the high absorption of light by hemoglobin (Hb), as well as the high level of scattering, present a similar problem, not allowing light to penetrate over a substantial distance. However, between approximately 700 nm and 900 nm, light readily penetrates most biological tissues (including bone) because the scattering and absorption of photons are relatively low. Because of these properties, this range has been characterized as an "optical window" that can be exploited for measurement purposes.

What makes this window especially promising from a measurement perspective is that, within this range, the two main forms of Hb, namely oxyhemoglobin (O_2Hb) and deoxyhemoglobin (HHb), exhibit distinguishable optical absorption characteristics (or *extinction spectra*; see Figure 1). Furthermore, O_2Hb and HHb,

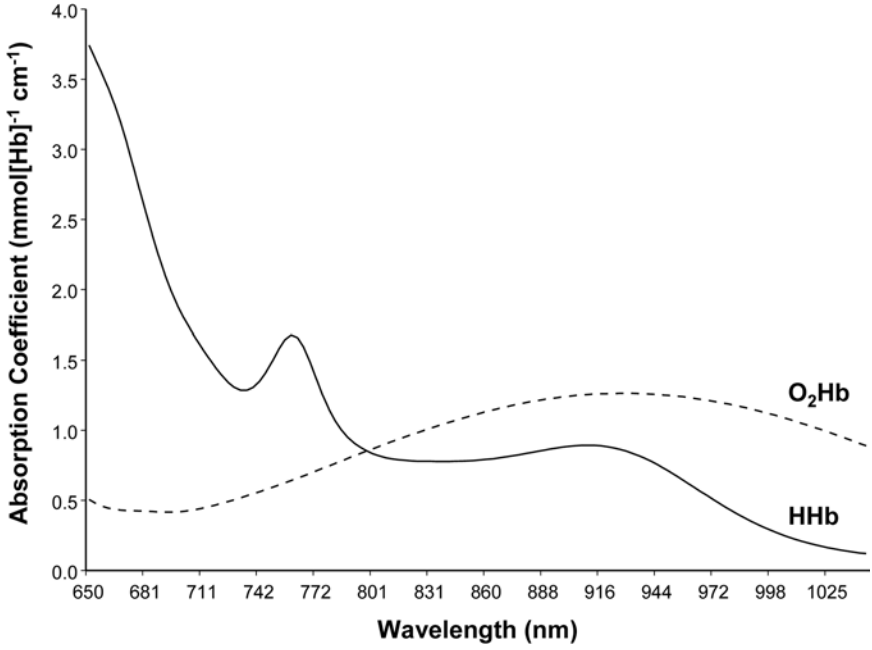

Figure 1 — Extinction spectra of O_2Hb and HHb in the near infrared window. Data from Wray et al. (1988).

along with water (whose concentration in normally hydrated biological tissues is assumed to be constant and estimated at 70%), constitute the main light absorbers, or *chromophores* (others—including lipids, cytochrome oxidase, and myoglobin—are less important quantitatively). An examination of the extinction spectra of O_2Hb and HHb (see Figure 1) shows that HHb exhibits an absorption peak that is clearly distinguishable from O_2Hb near 760 nm, whereas the absorption of O_2Hb peaks over a broader range but becomes distinguishable from HHb above approximately 830 nm (Wray, Cope, Delpy, Wyatt, & Reynolds, 1988).

Taking advantage of these properties of near-infrared light, the first application to the study of cerebral oxygenation was proposed over 30 years ago by Jöbsis (1977). The task of using near-infrared light to examine the concentration of O_2Hb and HHb within the brain is greatly complicated by the fact that the head is a heterogeneous medium consisting of layers of skin, skull, dura, cerebrospinal fluid, and cortical tissue with gyri and sulci. Whenever a ray of light (or photon) strikes a surface or crosses a boundary between media with different refractive properties (as when light enters the water), it changes the direction it was initially traveling. This is called *scattering*. Because of the varied tissues within the head, the proportion of photons that are scattered as they travel through the head is actually far greater than the proportion that is absorbed by chromophores. As will be explained in the next section, scattering must be measured or estimated before the absorption of near-infrared light by chromophores can be determined.

NIRS instruments work either in *transmission* or in *reflection* mode. The term *transmission mode* refers to light traveling through the sample (from one side to the other). This mode of operation is possible only when the object being investigated is of small diameter (e.g., a neonate head). It should be noted, however, that because of the widespread scattering in (heterogeneous) biological tissues, light does not travel in a straight line. For example, in an empirical investigation on the rat head using picosecond-length light pulses to estimate the "time of flight" of the photons through the medium in transmission mode, it was found that the first 5% of photons emerged after having traveled the equivalent of 2.6 times the head diameter and the last 5% after having traveled 9.2 times the equivalent of the head diameter (Delpy, Cope, van der Zee, Arridge, Wray, & Wyatt, 1988).

When the object is larger and transmission is not possible, the reflection mode is used (see Figure 2). In this case, the NIRS instrument emits light into the tissue and measures light emerging from the tissue several centimeters away. In reflection mode, light is presumed to travel between the emitter and detector following a crescent (semilunar) path (Gratton, Maier, Fabiani, Mantulin, & Gratton, 1994), with the apex of the curve being a few centimeters into the tissue (and the depth being directly proportional to the distance between the emitting and detecting fibers). This curved path results from two factors. First, as noted earlier, biological tissues cause significant scattering and scattering is much greater than absorption.

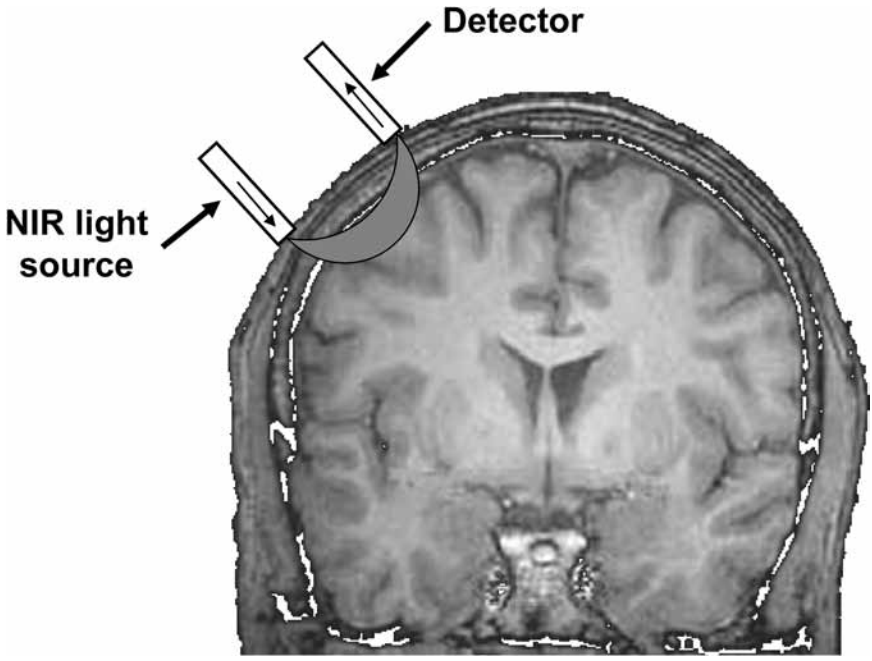

Figure 2 — An example of NIRS in reflection mode. Near infrared light propagates through the tissue sample in a crescent (semilunar) path, with the apex of the curve being a few centimeters into the tissue. The depth of penetration is directly proportional to the distance between the emitting and detecting fibers.

If the tissue caused no scattering, light would travel through the tissue in a straight line. If scattering was not much greater than absorption, all the light would be absorbed as it traveled through the tissue. In neither case would it have been possible to detect any remaining photons at the surface of the tissue. Second, as photons are "diffused" through a medium such as the human head, they can follow a theoretically infinite number of paths. However, photons that find themselves near the surface boundary (the skull and scalp) are more likely to be "lost" (exit the head). Thus, in actuality, for the photons that remain and can reach the detector, some of the photon paths are more likely than others, forming a *probability density function* that is more "dense" (more likely) along the crescent path from emitter to detector (Gratton et al., 1994).

The Modified Beer–Lambert Law

All NIRS methods are based on a theoretical *cuvette* model (see Figure 3). According to this model, a chemical compound of interest, which absorbs light, is dissolved in a solvent that does not absorb light (and neither does the glass cuvette that contains the compound and the solvent). As an interrogating beam of light (of a wavelength specific to the extinction characteristics of the compound of interest) is emitted into the cuvette from one side, some of the photons are absorbed by the compound. Thus, the light that emerges from the other side of the cuvette is of reduced intensity. The difference between the intensity of the initial and the emergent light can be used as a measure of the concentration of the compound of interest. The Beer–Lambert law (Hoshi, 2005; Rolfe, 2000; Villringer & Obrig, 2002), which applies to this simplified case, states that the attenuation of light transmitted through an absorbing compound dissolved in a nonabsorbing solvent is directly proportional to the product of (a) the concentration of the compound and (b) the optical path length (i.e., the length of material that the light travels through). Thus, attenuation A can be given by the formula

$$A = \log(I_0/I) = \varepsilon\,[c]\,l$$

where I_0 is the intensity of light entering the material (*incident intensity*), I is the (reduced) intensity of light measured exiting the material, ε is the extinction coefficient of the compound of interest, l is the optical path length, and $[c]$ is the concentration of the compound of interest.

Obviously, biological tissues represent a much more complex sample than what is described by the cuvette model. For example, this model disregards scattering and assumes the presence of a single light-absorbing compound in the sample. In biological tissues, scattering is a pronounced phenomenon and, as a result, as noted earlier, the actual length of the path that light has to travel can be several times the physical distance between emitter and detector.

To account for the longer path length, a correction factor, termed *differential path-length factor* (DPF), is introduced. In addition, a second modification is needed to account for the fact that, when a variety of materials intervene between emitter and detector, a multitude of scattering patterns may occur. As a result of scatter, some photons may be scattered out of the emitter–detector path but the detector has no way of distinguishing between photons lost to absorption and

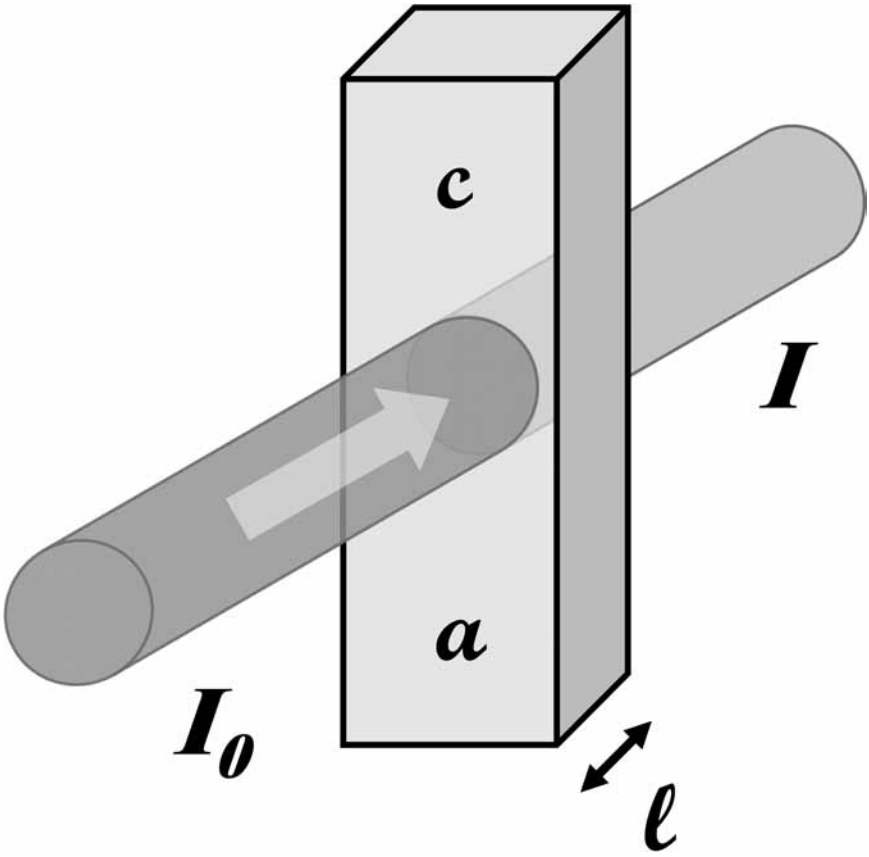

Figure 3 — The "cuvette" model, which forms the basis of the Beer–Lambert law. The initial intensity of light is indicated by I_0, the (attenuated) intensity of light that emerges from the cuvette is indicated by I, the optical path length (the length of material that light travels through) is indicated by l, the attenuation of light as it travels through the cuvette is indicated by a, and the concentration of the compound of interest in the cuvette is indicated by c.

photons lost to scattering beyond the range of the detector. Consequently, to account for the loss of photons as a result of scattering, a correction factor g is introduced that represents the mean cosine of the scatter angle. For example, $g = 1$ (the cosine of 0°) would represent forward scatter, $g = 0$ (the cosine of 90°) would represent lateral scatter, and $g = -1$ (the cosine of 180°) would represent backscatter. Thus, a modified Beer–Lambert law (Cope & Delpy, 1988; Delpy et al., 1988) incorporates these two modifications (see Figure 4):

$$A = \varepsilon\,[c]\,l\,\mathrm{DPF} + g$$

When dealing with samples containing more than one chromophore, such as O_2Hb, HHb, and H_2O, absorption at a particular wavelength λ would be given by

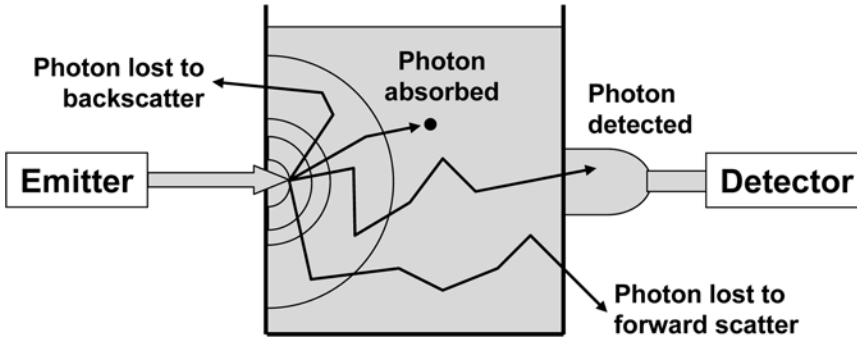

Figure 4 — A modified cuvette model, illustrating the concepts of photon absorption, forward and backward scatter, and differential path length (i.e., the nonlinear path from emitter to detector).

$$A_\lambda = \varepsilon_\lambda [O_2Hb]\, l\, DPF_\lambda + \varepsilon_\lambda' [HHb]\, l\, DPF_\lambda + \varepsilon_\lambda'' [H_2O]\, l\, DPF_\lambda + g_\lambda$$

The modified Beer–Lambert law makes three simplifying assumptions (Obrig & Villringer, 2003). First, because it is assumed that scatter is high but changes negligibly during the measurement, the DPF for a given wavelength remains constant. This assumption is considered tenable in NIRS measurements because, over time, changes in blood flow and, therefore, changes in Hb concentration and oxygenation will likely influence the absorption properties of the tissue more than its scattering properties.

Given the centrality of DPF in absorption calculations, several investigations have attempted to determine this parameter empirically. For example, van der Zee et al. (1992) used a dye laser to emit ultra-fast (less than 6 ps) light pulses (761 nm) into the heads of six men and four women in vivo (upper part of the forehead, just below the hair line) and a synchroscan streak camera to record the photons emerging from the sample. The mean distance traveled by the photons was divided by the distance between the optodes (emitter and detector) to calculate the experimentally derived DPF. These researchers found that the DPF was almost constant beyond an interoptode spacing of 2.5 cm, with a mean value of 5.93 ± 0.42 and no difference between men and women. Using an argon ion laser and a 40-mm distance between emitter and detector, Essenpreis et al. (1993) found a similar mean DPF value of 6.32 ± 0.46. Later, Zhao et al. (2002) extended these analyses and found that the DPF varied from 6.18 to 7.69 at the forehead, from 7.18 to 8.87 at the somatosensory motor region, and from 6.98 to 9.35 at the occipital region (at 759 nm, with a less than 10% decrease in these values as the wavelength increased to 834 nm). It should be noted, however, that estimates of the portion of the path length attributable to cerebral tissue, as opposed to extracerebral tissue, range widely—from 15% to 55%—and the issue is still the subject of some controversy (Young, Germon, Barnett, Manara, & Nelson, 2000). In particular, the fraction of the path length attributable to the adult skull could be substantial (Hueber et al., 2001; Young et al., 2000).

Second, it is assumed that the medium being examined with NIRS (e.g., the head) is homogenous. This assumption is clearly violated in measurements on biological tissue.

Third, it is assumed that the parameters of interest change homogeneously within the volume being sampled. This assumption is also false in the case of the brain, where activation (i.e., changes in O_2Hb and HHb) within the sampled volume is probably not global but rather focal (i.e., limited to highly localized regions). This can lead to errors that are explained next.

First, since the volume of tissue being sampled is probably larger than the volume of activated tissue (assuming that the cerebral cortex exhibits highly localized changes in activity), this "partial volume effect" (Obrig & Villringer, 2003) results in an underestimation of the magnitude of focal changes in the chromophores of interest.

Second, there is probably a layered effect, because the path of light is likely affected by such factors as the layer of cerebrospinal fluid (Fukui, Ajichi, & Okada, 2003) and the layer of cerebral vessels on the surface of the brain (Firbank, Okada, & Delpy, 1998). To address this problem, researchers have examined the effect of varying the distance between the light source and the detector because a wider separation should, theoretically, result in sampling from a deeper layer within the head (i.e., presumably more from the cortex than from the superficial layers of skin, skull, and cerebrospinal fluid). Consistent with this idea, using a simplified model of the head, consisting of two concentric spheres, Hiraoka et al. (1993) showed that the influence of superficial layers decreases as the distance between the source and the detector increases. Likewise, using more sophisticated, layered models of the adult human head (scalp and skull, cerebrospinal fluid, gray matter, white matter), Okada et al. (1997) found that a source-detector spacing between 15 mm and 25 mm results in the gray matter contributing at least 20–30% to the change in the detected NIRS signal. The geometries of the sulci and the boundary between the gray and white matter layers were shown to have a negligible effect on the optical path length. More recently, Kohri et al. (2002) reported that, in human heads in vivo, the estimated contribution of cerebral tissue to optical signals increased from 33% to 55–69% as the interoptode distance increased from 2 cm to 3 cm to 4 cm. Other in vivo investigations, using scalp ischemia and cerebral oligemia (reduction of blood supply) to manipulate extra- and intracerebral hemodynamics independently, have reached similar conclusions (Germon, Kane, Manara, & Nelson, 1994; Germon et al., 1998, 1999). For example, a study using an average interoptode separation of 4.7 cm showed that occlusion of scalp perfusion by an inflatable tourniquet had no significant effect on NIRS measurements, despite a significant drop in scalp blood flow measured by laser Doppler velocimetry (Owen-Reece, Elwell, Wyatt, & Delpy, 1996). Likewise, validation studies performed during carotid endarterectomy showed that, using interoptode distances of 4, 5, and 6 cm, cross-clamping of the internal carotid artery (which supplies blood to the brain) led to the expected fall in O_2Hb and rise in HHb, whereas cross-clamping of the external carotid artery (which supplies blood to the face, tongue, and external parts of the head) had no effect on NIRS measurements (Al-Rawi, Smielewski, & Kirkpatrick, 2001; Kirkpatrick et al., 1995; Mason, Dyson, Sellars, & Beard, 1994).

Third, because the optical properties of tissue are different at different wavelengths and, therefore, optical path length is wavelength dependent (Kohl et al., 1998), there may be "cross-talk" errors (Boas et al., 2001; Strangman, Franceschini, & Boas, 2003). Thus, a real change in O_2Hb could theoretically be accompanied by a pseudo-change in HHb and vice versa. However, Monte Carlo simulations by Uludag, Kohl, Steinbrink, Obrig, and Villringer (2002) showed that the cross-talk between O_2Hb and HHb resulted in error of approximately 10% of the observed changes in these chromophores. When the analysis was focused on two wavelengths commonly used in NIRS research (760 nm and 830 nm), the cross-talk error was only 2–3% in a homogeneous layered model (for a depth of 8–12 mm, corresponding to the upper part of the gray matter) and similarly small in a layered brain model. Thus, the authors concluded that "when only oxygenated and deoxygenated hemoglobin are regarded, the estimated cross-talk is small" and "might have hardly any significance in practical terms for quantification of hemoglobin" (p. 58). Uludag, Steinbrink, Villringer, and Obrig (2004) further reported that cross-talk error can be reduced consistently to less than 10% if one wavelength is between 650 and 720 nm and the other is between 730 and 920 nm. Yamashita, Maki, and Koizumi (2001) experimented with different combinations of wavelengths, fixing one at 830 nm (presumably reflecting O_2Hb) and varying the other (799, 782, 752, 692, 664 nm). They found that noise was consistently reduced as the second wavelength was decreased. Thus, the measurement of O_2Hb and HHb concentration changes were two times (in the case of O_2Hb) and six times (in the case of HHb) more precise by using the 830/664 nm pair than by using the 830/782 nm pair. Examining slightly different wavelengths (782, 750, 692, 678 nm) for pairing with 830 nm, Sato, Kiguchi, Kawaguchi, and Maki (2004) found that the highest signal-to-noise ratio was achieved with the 830/692 pair. On the basis of these experimental results, Boas et al. (2004) have more recently expressed the view that using the 690 and 830 nm pair "significantly reduces the sensitivity to cross-talk . . . although it will not guarantee that cross-talk will not appear" (p. S279).

Types of Instruments

There are three main types of NIRS instruments and the operating principles behind each type are represented graphically in Figure 5. The simplest approach to NIRS measurement involves continuous-wave (CW) light sources, usually at discrete wavelengths selected to correspond to the peaks of the extinction spectra of O_2Hb and HHb (Cope & Delpy, 1988). The only optical parameter that can be measured with CW instruments is attenuation. Because CW instruments do not allow for the measurement of the optical path length (see the modified Beer–Lambert law), they cannot provide absolute values of the concentration of chromophores but only relative changes in concentration (e.g., compared with baseline), expressed in arbitrary units (Delpy & Cope, 1997; Hoshi, 2003).

In time-resolved spectroscopy (TRS), light is emitted into the tissue in picosecond-length pulses and the emerging light is measured as a function of time, also with picosecond resolution (e.g., Chance et al., 1988; Delpy et al., 1988; Patterson, Chance, & Wilson, 1989). The detected mean transit time of photons pro-

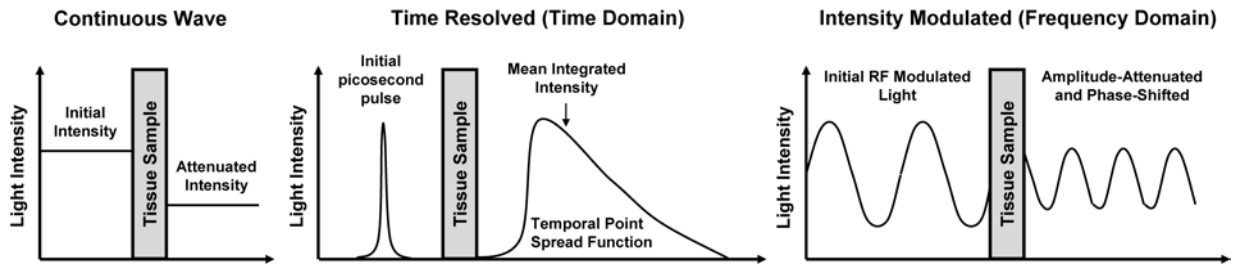

Figure 5 — Graphical illustration of the operating principles of the three main types of NIRS instruments (based on Delpy & Cope, 1997). In continuous wave (CW) instruments, light with a specific wavelength is emitted into the tissue and the intensity-attenuated light that emerges from the sample is measured. In time-resolved spectroscopy (TRS), a picosecond-length pulse of infrared light is emitted into the tissue and the photons that emerge from the sample as a function of time (also with picosecond resolution) are measured, to construct a temporal point spread function. In frequency-domain spectroscopy, light is emitted into the tissue not at a constant intensity (CW) or as a quick pulse (TRS) but as a sinusoidally modulated wave (i.e., intensity varying with time). The light that emerges from the tissue also shows this modulation but there is a phase delay, as well as attenuation as a result of the effects of absorption and scattering.

vides a measure of the mean optical path length. Although having an estimate of the optical path length overcomes the limitation of the CW approach, investigations of brain activation still face the problem of the unknown contribution of cerebral and extracerebral tissue to the optical path length. Furthermore, the practicality of TRS is limited somewhat by the size and cost of the instruments it requires (i.e., as described earlier, special ultrafast lasers and synchroscan cameras with picosecond resolution).

Frequency-domain approaches were developed to provide a more practical and inexpensive method for assessing the time it takes photons to propagate from emitter to detector (termed the *mean photon time of flight*) and, thus, the optical path length (e.g., Duncan et al., 1995; Fantini, Franceschini, & Gratton, 1994; Fantini et al., 1995; Lakowicz & Berndt, 1990). Light is emitted into the tissue not at a constant intensity (as in CW) or a short pulse (as in TRS) but rather as a sinusoidally modulated wave (i.e., intensity varying over time) at a radio frequency, usually 100–150 MHz (see Figure 6). The light that emerges from the tissue also shows this modulation but with a phase delay (as well as attenuation owing to scattering and absorption). This phase delay is proportional to the mean photon time of flight (Arridge, Cope, & Delpy, 1992).

A variation of the frequency-domain approach is the multidistance method (Gratton, Fantini, Franceschini, Gratton, & Fabiani, 1997). As noted earlier, as the intensity-modulated light travels away from its source, its amplitude is attenuated and its phase is delayed. An instrument can measure the constant (average) and the alternating component of the sinusoidal wave at two or more points between the light source and the detector, and can thus calculate the phase delay. By mea-

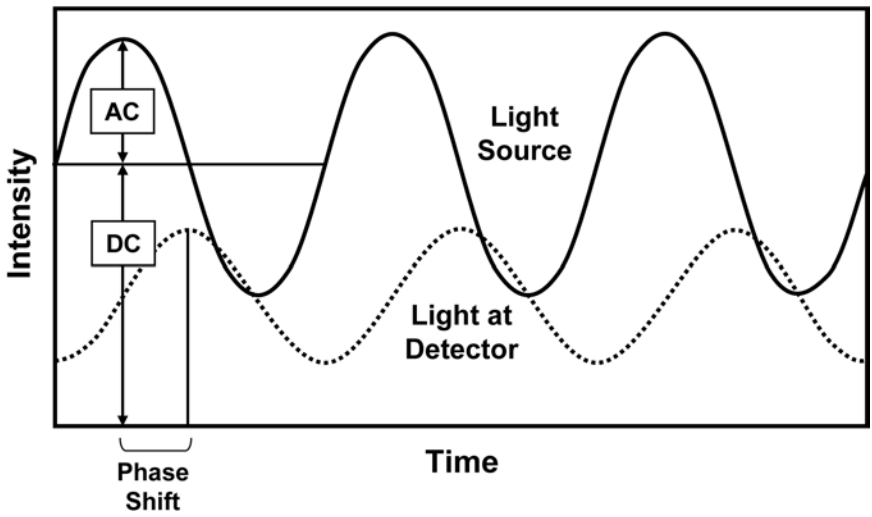

Figure 6 — Illustration of the sinusoidally modulated wave of light in and out of the tissue sample in frequency-domain spectroscopy. Multidistance instruments can measure the constant (average) and the alternating component of the sinusoidal wave, as well as the phase delay and, from these parameters, calculate the absorption and scattering coefficients.

suring how the constant component (DC), the alternating component (AC), and the phase change as a function of the distance between the source and the detector, the instrument can determine the absorption and scattering coefficients of the tissue being investigated. In the following equations (see Fantini et al., 1995; Fishkin & Gratton, 1993; Gratton et al., 1997), the quantities $\ln(R\ U_{DC})$, $\ln(R\ U_{AC})$, and Φ are linear functions of the source–detector distance R (i.e., all describe lines of the form $Y = aX + b$):

$$\ln(R\ U_{DC}) = R\ S_{DC}\ (m_a, m_s') + K_{DC}$$

$$\ln(R\ U_{AC}) = R\ S_{AC}\ (m_a, m_s') + K_{AC}$$

$$\Phi = R\ S_{\Phi}\ (m_a, m_s') + K_{\Phi}$$

In these equations, R is the interoptode distance, U_{DC} is the average photon density (the constant component of the sinusoidal wave), U_{AC} is the amplitude of the photon density oscillations (the alternating component of the sinusoidal wave), Φ is the phase lag between source and detector, m_a is the absorption coefficient, and m_s' is the scattering coefficient. The quantities K_{DC}, K_{AC}, and K_{Φ} are constants, independent of R. The slopes of the lines (the quantities S_{AC}, S_{DC}, and S_{Φ}) are functions of the absorption and scattering coefficients of the tissue and other parameters that are known or considered known (such as the modulation frequency and the speed of light in tissue). Once these slopes are found, m_a and m_s can be calculated from any one of the pairs of slopes (i.e., S_{DC} and S_{Φ}, S_{AC} and S_{Φ}, or S_{DC} and S_{AC}; for formulas, see Fantini, Franceschini, Fishkin, Barbieri, & Gratton, 1994; Gratton et al., 1997). Although measuring DC, AC, and Φ at two distances from the source suffices to determine S_{AC}, S_{DC}, and S_{Φ}, multidistance instruments typically do so at more distances (e.g., see Figure 7) and derive averages, thus improving accuracy and reliability (Steinbrink, Wabnitz, Obrig, Villringer, & Rinneberg, 2001) and reducing noise (particularly if the calculation of m_a and m_s is based on S_{AC} and S_{Φ}, because AC is less susceptible to background light than DC).

An advantage of the frequency-domain multidistance method is that it permits the direct assessment of the absorption and scattering properties of tissue and, thus, theoretically, the determination of the concentration of chromophores in absolute rather than relative units (following calibration with a sample of known optical properties). Another advantage is that, given the availability of data from more than two source–detector distances (i.e., the minimum necessary to calculate the slopes), researchers have the flexibility to disregard data obtained from the shorter distances, which presumably interrogate more superficial layers, and, thus, possibly attenuate the influence of extracerebral changes (Gratton et al., 1997; Hemelt & Kang, 1999).

Physiological Interpretation of NIRS Signals

One of the strengths of NIRS over most other techniques reviewed earlier in this article is that observed changes can be attributed to underlying physiological causes with a high degree of specificity (Villringer & Obrig, 2002). There is consensus that focal brain activation is accompanied by increases in regional cerebral

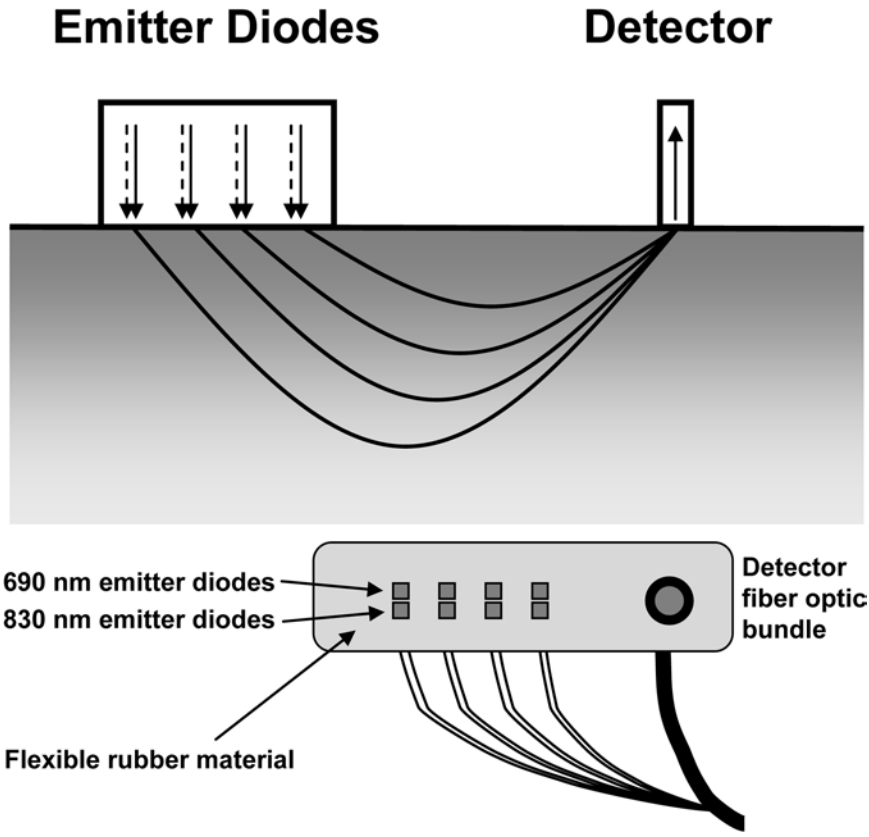

Figure 7 — The top panel shows the arrangement of the multiple emitter diodes and the detector in multidistance frequency-domain instruments. Because of the different distances between emitter and detector, this arrangement could provide information on the relative contribution of extra- and intracerebral influences on NIRS parameters. The bottom panel shows an example of a cranial sensor for a multidistance frequency-domain instrument.

blood flow (rCBF) and regional cerebral oxygen metabolic rate ($rCMRO_2$). However, although blood flow and metabolism had long been considered closely coupled and, therefore, essentially equivalent concepts, Fox and Raichle (Fox & Raichle, 1986; Fox, Raichle, Mintun, & Dence, 1988) discovered that they are not. Using PET, they found that the focal increase in rCBF induced by somatosensory and visual stimulation was much larger than the concomitant local increase in $rCMRO_2$ (approximately 30–50% versus 5%). Thus, O_2 delivery (O_2 content × CBF) increased, whereas the extracted fraction of available O_2 decreased. This phenomenon cannot be explained by an increased need for O_2 (Mintun et al., 2001) or glucose (Powers, Hirsch, & Cryer, 1996), and its apparent inefficiency remains a mystery.

Several models of "neurovascular coupling" have been proposed to solve this conundrum. According to one influential theory, O_2 metabolism is presumed to be

efficient (i.e., all or nearly all the O_2 that leaves the capillaries and is made available to brain cells is believed to be dissociated from O_2Hb and metabolized) but the relationship between rCBF and $rCMRO_2$ is nonlinear (Buxton, 2002; Buxton & Frank, 1997; Buxton, Wong, & Frank, 1998). This is because the observed increases in rCBF are assumed to reflect increases in flow velocity rather than the perfusion of additional capillaries. In turn, an increase in flow velocity means decreased capillary transit times and, because the probability of an O_2 molecule being transferred from the capillary to the mitochondrion is reduced with decreased transit times, this also leads to a reduction in the O_2 extraction fraction (i.e., the ratio of O_2 consumption to O_2 delivery). Thus, large increases in rCBF are required to support small increases in $rCMRO_2$ (i.e., there is still "coupling" but the relationship is exponential rather than linear). Even though this remains a viable hypothesis, several alternative or expanded models also exist (Raichle & Mintun, 2006).

Although the reasons for the apparent inefficiency (i.e., the large increase in rCBF and small increase in $rCMRO_2$) continue to puzzle researchers, it is precisely this inefficiency that has made functional brain imaging based on hemodynamic signals (i.e., PET, fMRI, NIRS) possible. Because of the mismatch between rCBF and $rCMRO_2$ and the associated reduction in the O_2 extraction fraction, neuronal activation is accompanied within a few seconds by a decrease in HHb and an increase in O_2Hb (Obrig & Villringer, 2003; Villringer & Dirnagl, 1995). The decrease in HHb is due to the fact that blood rich in O_2Hb (i.e., arterial blood) washes it out of the capillary bed. According to Raichle (2002), "Blood flow, whatever its cause, has a most remarkable and intimate relationship to the neuronal activity of the brain. This relationship permits us to go forward with functional brain imaging while, in parallel, we pursue answers to the challenging question of why the blood flow changes" (p. 17).

Within the NIRS literature, different authors have recommended focusing on different aspects of the circulatory and metabolic changes. For example, according to Obrig and Villringer (2003), an increase in O_2Hb may be consistent with the operational definition of cerebral activation but it may also reflect a change in blood pressure or an increase in skin blood flow (to the extent that the NIRS signal is influenced by such extracerebral factors). Thus, these researchers argue that "a decrease in HHb is the most valid parameter" (p. 9). On the other hand, according to Hoshi (Hoshi, 2005; Hoshi, Kobayashi, & Tamura, 2001), changes in HHb might reflect changes in venous blood oxygenation and volume rather than rCBF and, consequently, he suggests that "O_2Hb is the best indicator of changes in rCBF" (Hoshi et al., 2001, p. 1662).

Overall, it seems appropriate to suggest that all three parameters (O_2Hb, HHb, and total Hb) should be reported given that each may contribute an important piece of information, particularly in conjunction with the others. According to Obrig and Villringer (2003), if HHb increases in parallel with O_2Hb, this may reflect an artifact or a change in systemic or extracerebral hemodynamics (e.g., a Valsalva maneuver). If HHb increases but O_2Hb decreases, this would indicate deactivation (decrease in rCBF). In addition to O_2Hb, HHb, and total Hb, some derived parameters are also commonly reported as indices of oxygenation, including [O_2Hb] − [HHb] and the so-called tissue oxygenation index (Yoshitani et al., 2007), defined as the ratio of O_2Hb to total Hb (i.e., O_2Hb + HHb).

Perhaps one of the most intriguing features of NIRS is the now well-established relationship of HHb decreases to increases in the blood-oxygenation-level-dependent (BOLD) signal of fMRI (Ogawa, Lee, Kay, & Tank, 1990). This phenomenon can be explained by the fact that HHb has paramagnetic properties whereas O_2Hb does not (Pauling & Coryell, 1936). Although, given the current popularity of fMRI as a brain imaging method, the BOLD signal has been widely accepted as an index of "activation," in actuality, its exact physiological basis is not fully understood (Arthurs & Boniface, 2002; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001; Raichle, 2001; Ugurbil, Toth, & Kim, 2003). Thus, the observed inverse relationship between HHb and BOLD could help clarify the physiological basis of the BOLD signal (which is of benefit to fMRI research) and could help place NIRS data within the context of the much larger fMRI literature (which is of benefit to NIRS research). Because NIRS has (at present) better physiological specificity than fMRI, whereas fMRI has far superior spatial resolution and depth coverage, there is an ongoing effort to integrate the two techniques (Gratton, Toronov, Wolf, Wolf, & Webb, 2005; Obrig et al., 2000; Steinbrink et al., 2006; Toronov et al., 2003).

The close inverse relationship between HHb assessed by NIRS and the BOLD signal assessed by fMRI has been found in studies using finger opposition (Kleinschmidt et al., 1996), rhythmic finger tapping (Sassaroli, Frederick, Tong, Renshaw, & Fantini, 2006), finger tapping at maximal speed (Mehagnoul-Schipper et al., 2002), finger tapping at self-selected speed (Huppert, Hoge, Diamond, Franceschini, & Boas, 2006), four-finger flexion/extension (Strangman, Culver, Thompson, & Boas, 2002), light palm squeezing (Toronov, Webb, Choi, Wolf, Michalos et al., 2001; Toronov et al., 2003), apple peeling (Okamoto et al., 2004), breath holding (MacIntosh, Klassen, & Menon, 2003), and mental arithmetic (Toronov, Webb, Choi, Wolf, Safanova, et al., 2001), among others. It should be noted that studies have also shown a relationship between blood flow and volume assessed with PET and total Hb concentration assessed with NIRS, following hemodynamic challenges (Ohmae et al., 2006; Rostrup, Law, Pott, Ide, & Knudsen, 2002; Villringer et al., 1997).

Theoretical Questions in the Context of Exercise

There are numerous interesting theoretical questions within the context of exercise and physical activity that could be investigated using NIRS. Those presented here by no means constitute an exhaustive list. They were chosen merely as representative examples because they relate directly to the function of the prefrontal cortex and have been previously discussed in relation to exercise in the published literature.

One hypothesis that has received attention in exercise psychology is that the left and right prefrontal lobes are specialized for approach and withdrawal tendencies, respectively, and, consequently, an index of prefrontal hemispheric asymmetry should be related to approach-or-withdrawal behaviors and positive-or-negative affective responses (Davidson, 2004a, 2004b). In both general and exercise psychophysiological research, this idea has been investigated using an asymmetry index derived from EEG recordings. In this line of research, the alpha

frequency band (8–13 Hz) derived from the fast-Fourier transform of the raw EEG signal is considered a quantitative estimate of cortical deactivation (i.e., greater spectral power within the alpha band is presumed to be related to lower activity in the underlying layers of cerebral cortex, whereas less spectral power in the alpha band is presumed to be related to higher cortical activity). Although some authors have reported findings that support this hypothesis in the context of exercise, showing significant relationships between alpha-based prefrontal hemispheric asymmetry and postexercise self-reports of affect (e.g., Petruzzello et al., 2006; Petruzzello, Hall, & Ekkekakis, 2001), others have questioned the physiological significance of changes in the alpha band (Crabbe & Dishman, 2004). Recent research has used NIRS, instead of EEG, to test the laterality hypothesis using a transient anxiety–induction paradigm (Morinaga et al., 2007). The greater degree of physiological specificity of NIRS-based indices of cerebral activation compared with EEG alpha could help advance this line of research within the context of exercise. Importantly, the greater resistance to movement artifact afforded by NIRS compared with EEG offers the additional advantage of making meaningful during-exercise assessments of prefrontal cortical activity possible.

Another idea that appears highly amenable to testing using a NIRS-based approach is the transient hypofrontality hypothesis, which has been proposed as an explanation for exercise-induced positive affective changes (Dietrich, 2003, 2006). Specifically, it has been suggested that acute exercise may induce its anxiolytic and antidepressant effect by inhibiting excess activity in regions of the prefrontal cortex that constitute the neural basis of the cognitive antecedents of anxiety and depression. This is theorized to happen because—given that blood flow to the brain remains almost constant during exercise—a redistribution of metabolic resources might be necessary, and, as a result, more blood needs to be directed toward the high-priority homeostatic regulation centers than to the frontal cortical areas (which may be of relatively less importance under the circumstances). Indirect evidence in support of the hypofrontality hypothesis has come from studies showing that performance on neuropsychological tests theorized to specifically tap frontal cortical activity (e.g., the Wisconsin Card Sorting Task, the Paced Auditory Serial Addition Task, or the Stroop Test) was selectively impaired by exercise (Dietrich & Sparling, 2004). The limitations of inferences drawn from such indirect evidence are clear, so it has been suggested that "direct measures of transient hypofrontality are necessary to substantiate the hypothesis" (Dietrich, 2006, p. 82). NIRS has been used for the direct assessment of transient hypofrontality in other research (e.g., Fallgatter, Müller, & Strik, 1998) and could be used for this purpose in the context of exercise as well. In fact, NIRS is probably the safest and most practical method for assessing the function of the prefrontal cortex (through hemodynamic parameters) over different exercise intensities since movement artifact (EEG, fMRI) or high radiation exposure (PET, SPECT) would render other methods inappropriate for studies of this sort.

A third conceptual formulation that includes aspects testable through NIRS is the dual-mode theory (Ekkekakis, 2003; Ekkekakis & Acevedo, 2006; Ekkekakis, Hall, & Petruzzello, 2005a). According to this idea, affective responses to acute exercise are influenced jointly by top–down cognitive factors (such as self-efficacy for exercise) and bottom–up interoceptive afferents (such as muscular and respiratory cues). The relative importance of these two factors is hypothesized to

shift systematically as a function of exercise intensity. Specifically, cognitive factors, considered expressions of processes originating mainly in prefrontal cortical areas, are hypothesized to account for most of the variance in affective responses when the intensity presents a manageable (but still not overwhelming) challenge, namely, close to the ventilatory threshold. On the other hand, interoceptive factors are hypothesized to become increasingly salient as the intensity exceeds the level that permits the maintenance of a physiological steady state. As this happens, the multiple subcortical routes directing interoceptive information to the amygdala are believed to become the primary mode of affect induction (Ekkekakis & Acevedo, 2006). Several recent neuroimaging studies examining the neural substrates of the cognitive control of negative affect (all conducted in nonexercise contexts) have shown a reciprocal relationship between activity in the prefrontal cortex and activity in the amygdala (for reviews, see Ochsner & Gross, 2005, 2007). Although the activity of the human amygdala *during* exercise is still outside the reach of most neuroscience methods, a NIRS-based investigation of prefrontal cortical activity across the range of exercise intensity, in conjunction with this recent evidence, could provide insights into the limits of cognitive control over affective responses to exercise.

NIRS-Based Investigations of Cortical Hemodynamics in Exercise Research

NIRS technology has been used in exercise science for several years but has been applied mainly to the noninvasive investigation of the hemodynamics of the working muscle (e.g., Bhambhani, 2004; Boushel et al., 2001; Neary, 2004; Pereira, Gomes, & Bhambhani, 2007; Quaresima, Lepanto, & Ferrari, 2003; for a recent exception, see Perrey, 2008). Whenever NIRS-based data are discussed in the context of the cerebral metabolic response to exercise, these data are presented as being representative of global rather than regional changes (Dalsgaard, 2006; Ide & Secher, 2000; Nybo & Secher, 2004; Nybo & Rasmussen, 2007), although recent evidence has made it clear that changes can vary by cortical region (Subudhi, Miramon, Granger, & Roach, 2009). Moreover, practical rather than theoretical considerations seem to have dictated both the placement of NIRS sensors (i.e., placed on the forehead, to avoid distortions in NIRS signals due to hair) and the choice of the left-versus-right hemisphere (i.e., on the left hemisphere, since most study participants are right handed). In other words, questions about the functions that the underlying prefrontal cortex is theorized to support or issues of prefrontal hemispheric asymmetry and specialization (as summarized in the previous section) have not yet been raised in NIRS applications in the context of exercise. Nevertheless, an examination of the 28 studies summarized in Table 1 permits some preliminary conclusions (studies focusing on resistance exercise; static or isometric exercise; and simple motor tasks such as pinching, squeezing, or tapping were excluded from this analysis).

First, these studies convincingly demonstrate that NIRS assessments are feasible (i.e., with acceptable signal-to-noise ratios) during recumbent and upright cycle ergometry and even during treadmill walking and running. Of course, this should not be taken to imply that movement and other artifacts do not present a

potential challenge for NIRS assessments during vigorous exercise. Sudden head movements or frontalis muscle contractions may cause the NIRS sensors to shift, lose contact with the skin, and permit the influx of ambient light, thus leading to sharp increases in NIRS signals. Consequently, the use of appropriate head bands, probe holders, or caps is recommended, in conjunction with the use of medical adhesives for forming a secure bond between the sensor and the skin (e.g., Bonding Cement by Torbot of Cranston, RI; or 7730 Medical Adhesive by Hollister of Libertyville, IL). Furthermore, the position of the head (e.g., tilt) should not change during data collection, as this may cause blood shifts toward or away from the area being monitored, resulting in increases or decreases in NIRS signals that can easily be confused for hemodynamic responses associated with brain activation. Sophisticated users may also want to consider automated routines for removing artifact associated with bodily movements (Izzetoglu, Devaraj, Bunce, & Onaral, 2005; Sato et al., 2006) or skin blood flow (Kohno et al., 2007).

Second, there is evidence from these NIRS studies that, in healthy participants, exercise increases the oxygenation of the prefrontal cortex, as suggested by changes in O_2Hb, total Hb, and O_2 saturation (see Table 1). However, there appears to be a threshold intensity for this effect, although what the threshold is remains unclear. For example, although Ide, Horn, and Secher (1999) reported increases in O_2Hb, HHb, and total Hb with 10 min at 30% VO_{2max} and Suzuki et al. (2004) found increases with just 90 s of walking at 3 and 5 $km \cdot h^{-1}$, other investigations have not shown increases with minimal exercise stimuli. For instance, increasing intensity to 25% of peak power (Subudhi et al., 2007) or exercising for 3 min at 60% VO_{2max} (Nielsen, Boesen, & Secher, 2001), a 3-min step test (Saito et al., 1999), 15 min at 40% VO_{2max} (González-Alonso et al., 2004), or consecutive 5-min bouts at 30% and 50% VO_{2max} (Imray et al., 2005) have not been found to produce significant effects on oxygenation parameters. In contrast, increasing the intensity between 25% and 75% of peak power (Subudhi et al., 2007; Subudhi, Lorenz, Fulco, & Roach, 2008) or exercising for 10 min at 60% VO_{2max} (Ide et al., 1999) or for 5 min at 70% VO_{2max} (Imray et al., 2005) or slightly increasing breathing resistance while exercising for 3 min at 60% (Nielsen et al., 2001) can significantly increase the oxygenation of the prefrontal cortex. In a recent study by Timinkul et al. (2008), changes in O_2Hb across the stages of an incremental protocol on the cycle ergometer were analyzed not only for the entire group (N = 10), but also for each individual participant. This analysis showed that the level of intensity at which O_2Hb begins to increase varies considerably between individuals, both in terms of the percentage of maximal capacity and in relation to the lactate threshold. The heterogeneity of response patterns (both between and within studies) and the inability to link the increase in oxygenation to other cardiovascular or metabolic events raise the strong possibility that the increase in oxygenation reflects highly individualized patterns of neuronal activity in the prefrontal cortex. Thus, understanding the functions that the prefrontal cortices perform during exercise will be an essential step in deciphering the hemodynamic changes detected with NIRS. Some suggestions based on psychological theorizing are offered in the next section.

Third, there is also evidence from this literature that the increase in oxygenation does not continue linearly until exhaustion, but instead, a decreasing phase starts before the point of exhaustion (see Table 1). This has been found with 6 min

Table 1 Summary of 28 Studies in Which NIRS Has Been Used to Investigate Cerebral Hemodynamics During Dynamic Exercise. (Note that studies focusing on resistance exercise; static or isometric exercise; and simple motor tasks such as pinching, squeezing, or tapping were excluded from this summary.)

Study and Sample (Gender; Age; VO_{2max})	Experimental Conditions (Exercise Stimuli, Experimental Manipulations)	NIRS (Device, Interoptode Distance (If Given), Cerebral Region)	Summary of Findings
Ainslie et al. (2007) 6 male, 8 female; 25 years; 57 $mL \cdot kg^{-1} \cdot min^{-1}$	cycle ergometer, 60–70% VO_{2max} for 5–6 min, then hypoxia (O_2 from 21% to 14%) for 4–5 min, then normoxic recovery for 3–4 min	NIRO 300, interoptode distance 5 cm, "right side of the forehead"	At rest, hypoxia caused a gradual decrease in O_2Hb and an increase in HHb. During exercise, total Hb (mainly HHb and, to a lesser extent, O_2Hb) increased during hypoxia compared with normoxia.
Ainslie et al. (2008) 16 male, 12 female; 26 years; 55 $mL \cdot kg^{-1} \cdot min^{-1}$	cycle ergometer, 60–70% VO_{2max} for 5–6 min, then hypoxia (O_2 from 21% to 14%) for 4–5 min, then normoxic recovery for 2–3 min	NIRO 200, interoptode distance 5 cm, "right side of the forehead"	The experimental conditions included (a) 10–12 d of intermittent hypoxia + 12 d of continuous hypoxia (1560 m altitude), (b) 12 d of continuous hypoxia, (c) 11 d of intermittent hypercapnia. Exercise tests were performed at baseline, after intermittent hypoxia, after continuous hypoxia, 12–13 d after continuous hypoxia. Cerebral oxygenation during exercise was reduced in response to hypoxia. Following intermittent and/or continuous hypoxia, there was even larger reduction in cerebral oxygenation during hypoxic exercise. There was no change to the sensitivity of cerebral oxygenation to hypercapnia after any of the interventions. Intermittent hypercapnia produced no changes.

(continued)

Table 1 *(continued)*

Study and Sample (Gender; Age; VO_{2max})	Experimental Conditions (Exercise Stimuli, Experimental Manipulations)	NIRS (Device, Interoptode Distance (If Given), Cerebral Region)	Summary of Findings
Bhambhani et al. (2007) 17 male, 27 years; 38.8 $mL \cdot kg^{-1} \cdot min^{-1}$	ramp (30 W every 2 min) cycle ergometer protocol to exhaustion	MicroRunman, interoptode distance 4 cm, "over the left prefrontal lobe, approximately 3 cm from the midline and just above the supraorbital ridge	The difference between O_2Hb and HHb was considered an index of cerebral oxygenation and the sum (total Hb) was considered an index of cerebral blood volume. Both cerebral oxygenation and blood volume increased gradually until the respiratory compensation threshold and then decreased until VO_{2max}. However, the peak in these NIRS variables followed the respiratory compensation threshold with a slight delay in all but two participants (20 s in six, 40 s in eight, 60 s in one).

(continued)

Table 1 *(continued)*

Study and Sample (Gender; Age; VO_{2max})	Experimental Conditions (Exercise Stimuli, Experimental Manipulations)	NIRS (Device, Interoptode Distance (If Given), Cerebral Region)	Summary of Findings
González-Alonso et al. (2004) 6 male, 25 years; 4.7 $L \cdot min^{-1}$	cycle ergometer, 15 min at 40% VO_{2max}, max trials (360 W) under normal and elevated (+1 °C) core temperature	NIRO 500, "forehead"	Time to exhaustion was 5.8 min under elevated temperature and 1.0 min longer under normal temperature. During submaximal exercise and the first 90 s of maximal exercise, there were no significant changes in cerebral oxygen saturation in either temperature condition. Thereafter, regardless of temperature, cerebral oxygen saturation declined significantly but the arterial–venous O_2 difference across the brain (an index of brain O_2 uptake) increased by approximately 45%. Given that the middle cerebral artery mean velocity declined only 10–15% after the first 90 s of maximal exercise, only part of the enhanced O_2 uptake could be attributed to a compensatory mechanism associated with a decrease in global cerebral blood flow. Given that brain O_2 uptake at exhaustion did not exceed 45–48%, in contrast to the 91% reached by leg skeletal muscles, the data indicated that the brain maintains a large O_2 reserve, apparently as a protection mechanism against reductions in O_2 delivery.

(continued)

Table 1 *(continued)*

Study and Sample (Gender; Age; VO_{2max})	Experimental Conditions (Exercise Stimuli, Experimental Manipulations)	NIRS (Device, Interoptode Distance (If Given), Cerebral Region)	Summary of Findings
Ide et al. (1999) 2 female, 10 male; 23 years; 43 $mL \cdot kg^{-1} \cdot min^{-1}$	recumbent cycle ergometer, 30%, 60% VO_{2max} for 10 min each	NIRO 500, interoptode distance 4.5 cm, "on the forehead"	O_2Hb, HHb, and total Hb increased significantly during both intensities compared with rest. This apparent hyperoxygenation was interpreted as an increase in cerebral blood flow (parallel to an observed increase in middle cerebral artery mean blood velocity determined by transcranial Doppler) in excess of O_2 demand. This phenomenon could not be attributed to a reduced cerebral metabolic rate (since there was an increase in carbohydrate uptake by the brain during exercise) or to an increase in hematocrit.
Imray et al. (2005) 1 female, 10 male; 32–65 years; 43 $mL \cdot kg^{-1} \cdot min^{-1}$	fully supine cycle ergometer, at altitudes of 150, 3610, 4750, 5260 m; consecutive 5-min bouts at 30%, 50%, 70% VO_{2max}, ramp (20 $W \cdot min^{-1}$) to exhaustion	Critikon 2020, interoptode distance 10 & 37 mm, right frontoparietal region (3 cm from midline, 3 cm from supraorbital crest)	At 150 m, cerebral oxygen saturation showed little change from rest (68.4%) to submaximal exercise (70.9%) to maximal (69.8%). On the other hand, the levels were lower at higher altitudes and there were decreases with increasing intensity (at 3610 m: 66.2–61.2%, at 4750 m: 63.0–59.4%, at 5260 m: 62.4–58.0%). In most cases, there were gradual increases in total Hb during submaximal exercise, followed by a decrease from 70% to VO_{2max}. This pattern was accompanied by similar changes (i.e., increases during submaximal, decreases at maximal) in both O_2Hb and HHb. Middle cerebral artery mean velocity data showed peaks in O_2 delivery at 30–50% VO_{2max} and subsequent declines.

(continued)

Table 1 *(continued)*

Study and Sample (Gender; Age; VO_{2max})	Experimental Conditions (Exercise Stimuli, Experimental Manipulations)	NIRS (Device, Interoptode Distance (If Given), Cerebral Region)	Summary of Findings
Marshall et al. (2008) 6 male, 2 female; 27 years & 33 years (2 groups); 65.9 & 68.1 $mL \cdot kg^{-1} \cdot min^{-1}$	cycle ergometer test to exhaustion, starting from 3.33 $W \cdot kg^{-1}$, increasing 50 W for males, 25 W for females every 150 s	NIRO 200, interoptode distance 5 cm, "left forehead"	Participants were divided into 2 groups: (a) intermittent hypoxic exposures for 10 days or (b) placebo control. Tissue oxygenation index (O_2Hb / total Hb) decreased near exhaustion, starting at 60–80% VO_{2peak}. The placebo intervention showed no effects. In the intermittent hypoxia group, cerebral O_2Hb and HHb were higher at exhaustion postintervention but tissue oxygenation index was lowered (6.1% at 90% VO_{2peak} and 3.7% at 100% VO_{2peak}).
Nielsen et al. (1999) 11 male oarsmen; 24 years; 5.0 $L \cdot min^{-1}$	6-min all-out row under increased inspired O_2 fraction (30%) or control (21%)	INVOS 3100, "on the forehead just below the hairline"	Under control conditions, cerebral oxygen saturation (ratio of O_2Hb to total Hb) decreased 17%, HHb increased, and O_2Hb decreased. O_2 supplementation did not significantly affect the changes in HHb and O_2Hb but did maintain cerebral oxygen saturation to levels similar to rest. On the other hand, pH and muscle oxygenation were not affected by O_2 supplementation. Thus, the observed 2.4% increase in work capacity under O_2 supplementation (and the unanimous verdict that the exercise "felt better") was attributed to the effect of this intervention on cerebral rather than muscular oxygenation.

(continued)

Table 1 *(continued)*

Study and Sample (Gender; Age; VO_{2max})	Experimental Conditions (Exercise Stimuli, Experimental Manipulations)	NIRS (Device, Interoptode Distance (If Given), Cerebral Region)	Summary of Findings
Nielsen et al. (2001) 8 male, 24 years; 3.7 $L \cdot min^{-1}$	cycle ergometer, 3 min at 60% VO_{2max} (150 W), with breathing tube diameter of 30, 14, 10, 4.5, 3 mm; 3 min recovery; ramp (100 $W \cdot min^{-1}$) to exhaustion	NIRO 500, "on the forehead just below the hairline"	HHb, O_2Hb, and total Hb were not influenced by exercise under unrestricted breathing conditions. Total Hb and HHb progressively increased with increasing breathing resistance. On the other hand, O_2Hb increased under conditions of light and moderate breathing resistance but decreased at the highest level. During recovery, total Hb and HHb were significantly reduced and O_2Hb was increased. Finally, during the ramp to exhaustion, total Hb and O_2Hb decreased, whereas HHb increased. Given that global cerebral blood flow is unlikely to change during exercise, the increases in O_2Hb and total Hb observed during even light breathing resistance (leading to small increases in $PaCO_2$) were interpreted as indicating increases in regional cerebral blood flow in the frontal region.
Rao et al. (2009) 9 male, 10 female; 9–20 years	ramp treadmill protocol to voluntary exhaustion	INVOS 5100C, interoptode distance 4 cm, "on the midline forehead"	Average test duration was 13.3 ± 2.7 min. Cerebral O_2 saturation was unchanged before the ventilatory threshold. A decrease began after the ventilatory threshold. The lowest value corresponded with voluntary exercise termination in all cases.

(continued)

Table 1 *(continued)*

Study and Sample (Gender; Age; VO_{2max})	Experimental Conditions (Exercise Stimuli, Experimental Manipulations)	NIRS (Device, Interoptode Distance (If Given), Cerebral Region)	Summary of Findings
Rupp & Perrey (2008) 13 male, right-handed, cyclists or triathletes; 25 years; 75 $mL \cdot kg^{-1} \cdot min^{-1}$	ramp (30 $W \cdot min^{-1}$) cycle ergometer protocol to exhaustion	NIRO 300, interoptode distance 5 cm, "over the left prefrontal cortical area between Fp1 and F3 of the modified International EEG 10-20 system"	Total Hb increased until the respiratory compensation threshold and then reached a plateau, HHb increased throughout the test, and O_2Hb increased until the respiratory compensation threshold and decreased thereafter, until VO_{2max}. Thus, the $[O_2Hb]$–[HHb] difference, which was used as an index of cerebral oxygenation, also increased until the respiratory compensation threshold and decreased thereafter. However, the authors noted that, even though changes in end-tidal CO_2 mimicked those in cerebral oxygenation, the two variables were not significantly correlated. They concluded that the reduction in cortical oxygenation at the point of volitional exhaustion may play a "pivotal role" in the "integrative decision to stop exercise" (p. 162).
Saito et al. (1999) 12 male, 8 female (divided in two groups); 31 years	3-min step test (23 cm); one group at 2700 m, the other at 3700 m	INVOS 3100, interoptode distances of 3 and 4 cm, "forehead"	Cerebral O_2 saturation values during rest at sea level, 2700 m, and 3700 m were almost identical. O_2 saturation was not reduced during exercise at sea level but it was reduced after exercise at 2700 m (26.9%) and 3700 m (48.1%).

(continued)

Table 1 *(continued)*

Study and Sample (Gender; Age; VO_{2max})	Experimental Conditions (Exercise Stimuli, Experimental Manipulations)	NIRS (Device, Interoptode Distance (If Given), Cerebral Region)	Summary of Findings
Seifert et al. (2009) 8 male; 27 years; "all engaged in sports"	two incremental stationary cycling tests to exhaustion (60 W every fifth minute), 1 hr recovery	INVOS, interoptode distances of 3 and 4 cm, "at the forehead over the right frontal cortex"	Before and during the second test, participants were administered the beta blocker propranolol (0.15 $mg \cdot kg^{-1}$) intravenously to reduce heart rate by ~10 $beats \cdot min^{-1}$. Under control conditions, cerebral oxygen saturation increased nonsignificantly until 180 W, decreased until exhaustion, and increased again during 15 min of recovery. During beta blockade, cerebral oxygen saturation was reduced compared with control, especially at the point of exhaustion.
Shibuya, Tanaka, Kuboyama, Murai, et al. (2004) 5 male; 24 years; 48 $mL \cdot kg^{-1} \cdot min^{-1}$	stationary cycling at 120% VO_{2max} to exhaustion (duration 147.2 ± 3.4 s)	BOM-L1 TR, interoptode distance 5 cm, "over the forehead"	Cerebral oxygenation was defined as $[O_2Hb] - [HHb]$. Cerebral oxygenation, total Hb, and O_2Hb showed continuous decreases, whereas HHb showed a continuous increase from the 30th second to exhaustion.
Shibuya, Tanaka, Kuboyama, & Ogaki (2004) 6 male; 27 years; 43 $mL \cdot kg^{-1} \cdot min^{-1}$	7 cycles of supramaximal stationary cycling (30 s at 150% VO_{2max}, 15 s rest)	BOM-L1 TR, interoptode distance 5 cm, "over the forehead"	Cerebral oxygenation was defined as $[O_2Hb] - [HHb]$. Cerebral oxygenation and O_2Hb showed continuous decreases, whereas total Hb and HHb showed curvilinear responses, with decreases until the fifth (total Hb) or fourth (HHb) cycle and subsequent increases.

(continued)

Table 1 *(continued)*

Study and Sample (Gender; Age; VO_{2max})	Experimental Conditions (Exercise Stimuli, Experimental Manipulations)	NIRS (Device, Interoptode Distance (If Given), Cerebral Region)	Summary of Findings
Subudhi et al. (2007) 13 male cyclists; 30 years; 61 $mL \cdot kg^{-1} \cdot min^{-1}$	cycle ergometer, incremental test to exhaustion while breathing either normoxic (21% O_2) or hypoxic (12% O_2) gas	Oxymon, interoptode distance 4.26–4.61 cm, "over the left frontal cortex region of the forehead"	VO_{2peak} was reduced 37% and peak power was reduced 29% under hypoxia. Under normoxia, O_2Hb, HHb, and total Hb remained unchanged from rest to 25% of peak power but all three were significantly increased from 25% to 75% of peak power (indicating an increase in cerebral blood volume). This was followed by evidence of decreased oxygenation between 75% and 100% of peak power (i.e., decrease in O_2Hb, increase in HHb, and stable total Hb). This decrease was found in all participants. Under hypoxia, cerebral oxygenation showed a gradual decline throughout the test (i.e., decrease in O_2Hb, increase in HHb). On the other hand, total Hb was increased until 75% of peak power and then reached a plateau. The authors concluded that reduced cerebral oxygenation is unlikely to be a limiting factor in incremental exercise performance in normoxia (except within "a complex, integrative model of fatigue," p. 182) but it may play an important role in hypoxia.

(continued)

Table 1 *(continued)*

Study and Sample (Gender; Age; VO_{2max})	Experimental Conditions (Exercise Stimuli, Experimental Manipulations)	NIRS (Device, Interoptode Distance (If Given), Cerebral Region)	Summary of Findings
Subudhi et al. (2008) 11 male; 21 years; 3.98 $L \cdot min^{-1}$	cycle ergometer, 100, 130, 160 W, then 15 $W \cdot min^{-1}$ to exhaustion, then 60% O_2, at sea level, 1 h hypobaric hypoxia, 5 d hypobaric hypoxia	Oxymon MkII, interoptode distance 4.5 cm, "over the left frontal cortex region of the forehead"	At sea level, O_2Hb and total Hb increased from rest to moderate intensity, but from 75% to 100% of peak power, there was an increase in HHb and total Hb. After the switch to 60% O_2, total Hb decreased. Changes in total Hb were correlated with middle cerebral artery mean velocity positively (.61) until 75% peak power but negatively (−.86) from 75% to 100%. In both acute and chronic hypoxia, oxygenation fell throughout exercise. O_2Hb was lower and HHb was higher at all workloads compared with sea level (total Hb was similar). After the switch to 60% O_2, O_2Hb rose and HHb fell. Changes in total Hb were correlated with middle cerebral artery mean velocity positively (.71 and .82) until 50% peak power but negatively (−.78 and −.85) from 75% to 100%. The strong negative correlations between middle cerebral artery mean velocity and total Hb in the frontal lobe at high work rates was described as "a seemingly paradoxical finding that emphasizes the regional specificity of cerebrovascular regulation" (p. H169).

(continued)

Table 1 *(continued)*

Study and Sample (Gender; Age; VO_{2max})	Experimental Conditions (Exercise Stimuli, Experimental Manipulations)	NIRS (Device, Interoptode Distance (If Given), Cerebral Region)	Summary of Findings
Subudhi et al. (2009) 23 male, 2 female; 29 years; 3.49 $L \cdot min^{-1}$	incremental cycle ergometer test to exhaustion (25 W per min ramp) under normoxia and hypoxia	Oxymon III, 2 configurations: (a) "forehead over the left prefrontal cortex" (Fp1), (b) "left and right prefrontal cortex" (Fp1, Fp2) & "left premotor and motor cortices" (C1)	In normoxia, the tissue oxygenation index (O_2Hb / total Hb) remained relatively stable up to 75% of max but fell by an average of 9% thereafter as a result of large increases in HHb relative to O_2Hb. In hypoxia, the tissue oxygenation index was lower at rest compared with normoxia and fell throughout exercise by 26.5% owing to larger reductions in O_2Hb compared with normoxia. In normoxia, bilateral changes in prefrontal oxygenation were highly correlated (but O_2Hb and total Hb were slightly higher on the right than left at exhaustion). The correlations were also strong between prefrontal and premotor/motor regions for total Hb and HHb but not O_2Hb. Reductions in O_2Hb in the motor cortex were inversely correlated with the prefrontal regions ($R = -0.43$). In hypoxia, cerebral oxygenation again showed strong correlations between regions (but O_2Hb and total Hb were slightly higher in the right than left prefrontal cortex). Increased HHb was higher in the prefrontal cortex than the premotor/motor cortex.
Timinkul et al. (2008) 10 male, 21.4 years; 47.3 $mL \cdot kg^{-1} \cdot min^{-1}$	incremental cycle ergometer test to exhaustion (25 W every 3 min until 150 W, 25 W every min thereafter)	NIRO 300, "forehead"	As the workload increased, the tissue oxygenation index (O_2Hb / total Hb) showed a small increase (2–7%) but began to decrease gradually before exhaustion. O_2Hb increased at different points in relation to the lactate threshold for different individuals but the increase in all cases preceded the lactate threshold.

(continued)

Table 1 *(continued)*

Study and Sample (Gender; Age; VO_{2max})	Experimental Conditions (Exercise Stimuli, Experimental Manipulations)	NIRS (Device, Interoptode Distance (If Given), Cerebral Region)	Summary of Findings
Clinical Samples			
Jensen et al., 2002 12 female, 1 male with severe pulmonary disease; 42–65 years	recumbent cycle ergometer, 6 W every third min until exhaustion, under normoxic (21% O_2) and hyperoxic (35% O_2)	NIRO 500, interoptode distance 4 cm, "on the forehead just below the hairline"	In normoxic conditions, HHb increased during low intensity and increased even further at peak. O_2Hb did not significantly change and, therefore, total Hb increased during exercise. In hyperoxic conditions, HHb was significantly lowered at rest but O_2Hb and total Hb were unaffected. During exercise, HHb was decreased below the resting level and O_2Hb was increased to a level higher than that observed during normoxia. Total Hb showed the same increase as in normoxia.
Koike, Hoshimoto, et al. (2004, 2006) 31 male, 4 female with idiopathic dilated cardiomyopathy; 57 years; 19 $mL \cdot kg^{-1} \cdot min^{-1}$; 22 healthy controls, 56 years, 27 $mL \cdot kg^{-1} \cdot min^{-1}$	upright cycle ergometer, symptom-limited ramp (10 $W \cdot min^{-1}$)	NIRO 300, interoptode distance 5 cm, "left side of forehead"	O_2Hb increased in 21 of 22 healthy controls (left ventricular ejection fraction 70%) during exercise, whereas it decreased in 15 of 35 patients with idiopathic dilated cardiomyopathy (left ventricular ejection fraction 38%). The difference in O_2Hb from peak to rest was correlated with left ventricular ejection fraction (.59) and with VO_{2peak} (.62).

(continued)

Table 1 *(continued)*

Study and Sample (Gender; Age; VO_{2max})	Experimental Conditions (Exercise Stimuli, Experimental Manipulations)	NIRS (Device, Interoptode Distance (If Given), Cerebral Region)	Summary of Findings
Koike, Itoh, et al. (2004) 18 male, 15 female patients with valvular heart disease; 63 years; 20 $mL \cdot kg^{-1} \cdot min^{-1}$; 33 healthy controls > 50 years	symptom-limited incremental test on upright cycle ergometer (10 $W \cdot min^{-1}$)	NIRO 300, interoptode distance 5 cm, "left side of forehead"	In healthy participants, O_2Hb increased during exercise and HHb showed little change. In patients with valvular disease, O_2Hb gradually decreased (in 15 of 33 patients), whereas HHb gradually increased. O_2Hb was also significantly lower in patients than in controls, showing negative correlations with VO_{2peak} (–.61), VO_2 at the gas exchange ventilatory threshold (–.46), the ratio of changes in VO_2 to changes in work rate (–.57), and the ratio of changes in minute ventilation to changes in VCO_2 (–.45).
Koike et al. (2007) 9 male, 1 female, patients with idiopathic dilated cardiomyopathy or ischemic cardiomyopathy; 62 years	upright cycle ergometer, ramp (10 $W \cdot min^{-1}$) to leg fatigue and/or shortness of breath; under normoxia (21% O_2) and hyperoxia (50% O_2)	NIRO 300, interoptode distance 5 cm, "left side of the forehead"	In normoxia, O_2Hb gradually decreased. In hyperoxia, the decrease in O_2Hb was eliminated. The change in O_2Hb from rest to peak during hyperoxia was significantly higher than during normoxia. HHb showed little change and was no different between normoxia and hyperoxia.
Nagayama et al. (2007) 69 patients with coronary artery disease, 40 patients with high blood pressure; 62 years	upright cycle ergometer, symptom-limited ramp (10 $W \cdot min^{-1}$)	NIRO 300, interoptode distance 5 cm, "left side of forehead"	42 patients had a cerebral artery stenosis score equal to or higher than 2, indicating a suspected or apparent abnormality, based on magnetic resonance angiography. O_2Hb during exercise decreased in 29 of these 42 patients. The brain ischemic score was significantly, albeit weakly (–.20), correlated with the change in O_2Hb during exercise.

(continued)

Table 1 *(continued)*

Study and Sample (Gender; Age; VO_{2max})	Experimental Conditions (Exercise Stimuli, Experimental Manipulations)	NIRS (Device, Interoptode Distance (If Given), Cerebral Region)	Summary of Findings
Neary et al. (2008) 6 female with chronic fatigue (39 years, 23.8 $mL \cdot kg^{-1} \cdot min^{-1}$), 8 female control (27 years, 33.0 $mL \cdot kg^{-1} \cdot min^{-1}$)	upright cycle ergometer, 60 W for 2 min, then 25 W increases every 2 min to exhaustion	NIRO 300, interoptode distance 5 cm, "over the left frontal lobe, 1 cm above the eyebrow and 1 cm to the left of the skull center"	For both groups, there was a gradual increase in O_2Hb and total Hb from rest until approximately 90% of time to exhaustion and then a leveling off to exhaustion. HHb continued to increase until exhaustion. The tissue oxygenation index (O_2Hb / total Hb) showed a gradual decrease as intensity increased to fatigue in both groups. At exhaustion the chronic fatigue group had a significantly higher tissue oxygenation index than the controls.
Nielsen et al. (2005) 5 male, 3 female, patients with liver cirrhosis; 38–65 years	semirecumbent cycle ergometer, 3 workloads to target heart rates of 90–95, 115–120, and 140 bpm (to exhaustion)	INVOS 3100, "on the forehead above the frontal sinuses"	Cerebral oxygenation increased in response to exercise and reached its highest level at the point of exhaustion.
Multichannel (Optical Topography) Studies			
Miyai et al. (2001) 4 male, 4 female, right-handed; 24–46 years	five 30-s cycles of (a) treadmill walking (1 $km \cdot h^{-1}$) & rest, (b) arm swings & rest, (c) dorsiflexion-plantar flexion of feet & rest, (d) imagery of gait	OMM-2001, 30 source-detector pairs, interoptode distance 3 cm	Walking activated the medial portion of the primary sensorimotor regions and supplementary motor areas bilaterally. No activation was found in prefrontal and parietal regions. During walking, there was little change in the presumed arm areas of the primary sensorimotor cortex despite arm swinging. During arm swings without walking, there was activation in the more lateral and rostral parts of the primary sensorimotor cortex than those activated by walking.

(continued)

Table 1 *(continued)*

Study and Sample (Gender; Age; VO_{2max})	Experimental Conditions (Exercise Stimuli, Experimental Manipulations)	NIRS (Device, Interoptode Distance (If Given), Cerebral Region)	Summary of Findings
Suzuki et al. (2004) 7 male, 2 female, right handed; 22–46 years	90 s each of treadmill walking at 3 and 5 $km \cdot h^{-1}$, running at 9 $km \cdot h^{-1}$, with 60 s rest in-between	OMM-2001, 42 source-detector pairs, interoptode distance 3 cm	Increases in O_2Hb and total Hb in the prefrontal cortex, premotor cortex, and medial sensorimotor cortex were seen before the start of the tasks, especially at 9 $km \cdot h^{-1}$ (the increases were similar between 3 and 5 $km \cdot h^{-1}$). Once the tasks started, O_2Hb decreased to baseline or below-baseline levels, particularly in the premotor cortex. Prefrontal cortex activation was more prominent during running at 9 $km \cdot h^{-1}$. Laterality of activation was inconsistent between participants but highly consistent within.

Note. NIRO 200, 300, and 500 by Hamamatsu Photonics, Hamamatsu, Japan; INVOS 3100 and 5100C by Somanetics, Troy, WI; Critikon 2020 by Johnson and Johnson Medical, Newport, UK; BOM-L1 TR by Omegawave, Tokyo, Japan; Oxymon by Artinis, Zetten, Netherlands; MicroRunman by NIM Inc, Philadelphia, PA; OMM-2001 by Shimatzu, Kyoto, Japan.

of all-out rowing (Nielsen, Boushel, Madsen, & Secher, 1999), a quick ramp to exhaustion (Nielsen et al., 2001), a slower ramp to exhaustion (Imray et al., 2005), cycling to exhaustion against a constant high resistance (González-Alonso et al., 2004), increasing intensity from 75% to 100% of peak power (Subudhi et al., 2007, 2008, 2009), successive intervals of supramaximal (150% VO_{2max}) cycling (Shibuya, Tanaka, Kuboyama, & Ogaki, 2004), and cycling at 120% VO_{2max} (for 147 s) to exhaustion (Shibuya, Tanaka, Kuboyama, Murai, & Ogaki, 2004). Importantly, the physiological landmark that may instigate the reversal from the increasing to the decreasing trend in oxygenation may have been identified by the recent studies of Bhambhani, Malik, and Mookerjee (2007) and Ruppe and Perrey (2008) as the respiratory compensation threshold. Bhambhani et al. (2007) observed that the pattern of cerebral oxygenation changes (i.e., an initial increase during the first 3/4 of an incremental protocol, followed by a decrease near maximum) resembles the changes in arterial carbon dioxide ($PaCO_2$). Because $PaCO_2$ decreases above the respiratory compensation point and $PaCO_2$ is known to influence cerebral oxygenation, they hypothesized (and demonstrated empirically) that the decreases in oxygenation start soon after the respiratory compensation point has been exceeded. However, the subsequent study by Ruppe and Perrey (2008) found that, although changes in end-tidal CO_2 (used as an estimate of $PaCO_2$) mimicked those in cerebral oxygenation, the two variables were not significantly correlated. Likewise, Subudhi et al. (2008) did not find a correlation at low work rates and found a strong *negative* correlation (−0.85) from 75% to 100% of peak power. Moreover, Bhambhani et al. (2007) noted that, when the relationship between cerebral oxygenation and respiratory compensation was examined on an individual basis, there was again considerable interindividual variability. Specifically, compared with the respiratory compensation threshold, the decrease in cerebral oxygenation was delayed by 20 s in six participants, by 40 s in eight participants, and by 60 s in one participant, whereas the two events coincided for two participants. Thus, it appears, once again, that there is difficulty in accounting for the variance in the onset of the reduction in cerebral oxygenation by changes in systemic physiological parameters. So, to repeat the conclusion of the previous point, the functions that the prefrontal cortices might perform in response to strenuous exercise should be considered.

Fourth, the decreases in cerebral oxygenation can occur even with minimal increases in exercise intensity when O_2 delivery is compromised (see Table 1). Evidence for this phenomenon has been found by increasing breathing resistance to high levels (Nielsen et al., 2001), exercising at high altitude (Imray et al., 2005; Saito et al., 1999), breathing hypoxic gas (Subudhi et al., 2007), as well as in patients with heart disease (Koike, Itoh et al., 2004; Nagayama et al., 2007), idiopathic dilated cardiomyopathy (Koike, Hoshimoto et al., 2004, 2006), and severe pulmonary disease (Jensen et al., 2002), although not liver cirrhosis (Nielsen, Secher, Clemmesen, & Ott, 2005).

A final methodological observation is that nearly all NIRS investigations conducted so far have used either incremental exercise tests to exhaustion or exercise periods of very short duration. The lengthiest bouts do not exceed 15 min (González-Alonso et al., 2004). Thus, one limitation of this literature is that it precludes direct inferences regarding the effects of most common exercise pre-

scriptions and it does not address whether the reported short-term hemodynamic changes would be maintained over longer exercise bouts.

Tentative Framework for Interpreting Hemodynamic Changes in the Prefrontal Cortex

Although none of the NIRS-based studies that have been conducted until now have tested a psychologically informed hypothesis, several authors have raised the possibility that the decreases in prefrontal activity at the high end of the exercise intensity spectrum may have implications for "central fatigue" and the desire to discontinue exercise (e.g., Bhambhani et al., 2007; Nielsen et al., 1999; Rupp & Perrey, 2008; Subudhi et al., 2007, 2008; also see Dalsgaard, 2006; Dalsgaard & Secher, 2007; Nybo & Rasmussen, 2007). These allusions have direct relevance to recently proposed integrative models of fatigue (Kayser, 2003; Noakes, Peltonen, & Rusko, 2001). These models have profound importance for exercise science because they consider the brain, as opposed to peripheral bioenergetic variables, as the limiting factor for exercise performance.

What could help propel this line of research forward at this stage is the infusion of theoretical ideas from affective neuroscience and exercise psychobiology regarding the role of the prefrontal cortex (including the significance of asymmetrical activation) in regulating and coping with negative affective responses, such as tension, distress, or fatigue. Some of the relevant ideas were summarized in the previous section. The fact that the oxygenation of the prefrontal cortex is not necessarily positively related to middle cerebral artery mean velocity or end tidal CO_2 (Ainslie et al., 2007; Rupp & Perrey, 2008; Subudhi et al., 2008) underscores that the regulation of prefrontal activity may be subject to highly localized factors. An important recent study by Subudhi et al. (2009), using NIRS sensors placed not only bilaterally over the prefrontal cortex, but also over the premotor and motor regions, showed that (a) in normoxic conditions, at the point of volitional exhaustion, increases in O_2Hb and total Hb were larger in the right than in the left prefrontal cortex; (b) correlations between O_2Hb in the left prefrontal and the premotor/motor cortex were weak (R^2 from 0.01 to 0.55); (c) reductions in O_2Hb in the motor cortex were inversely correlated with prefrontal regions ($R = -.43$, $p < .01$); and (d) in hypoxia, deoxygenation was greater in the prefrontal than in the premotor and motor regions. These data, which are the first on cerebral hemodynamic parameters from multiple sites across the full range of exercise intensity, are in direct contrast to the assumption that prefrontal oxygenation can be considered indicative of global cerebral oxygenation or that it is subject only to systemic or whole-brain regulatory influences. On the basis of these data, as well as the bulk of the evidence emerging from the functional neuroimaging literature, it seems reasonable to suggest that this assumption is untenable and should be reconsidered.

The NIRS-based studies reviewed in Table 1 collectively illustrate that prefrontal oxygenation follows an inverted-U (so-called *hormetic*) dose–response pattern, with low-dose facilitation and high-dose inhibition. In their effort to address what the prefrontal cortex "does," authors in exercise science have resorted to generic references to "higher-order cognitive functions," including integrating

"goal-directed behavior, task-related memory, sensory information, and motivation to plan motor movements" (Subudhi et al., 2009, p. 1156) or "modulation of motor output during exercise" (Seifert, Rasmussen, Secher, & Nielsen, 2009, p. 300). However, although the prefrontal cortex may indeed be capable of these functions, there is no easy way to explain why these particular functions would be stimulated at a certain exercise intensity (as oxygenation increases) and then inhibited at a higher intensity (as oxygenation decreases). So, what else does the prefrontal cortex "do" that would make sense to invoke at a certain intensity and revoke at a higher intensity (close to maximal capacity)?

Based on evidence from the neuroimaging literature, a likely function is the regulation of negative affect (i.e., the displeasure, the tension, and the sense of fatigue associated with high-intensity exercise). As several theorists have suggested, negative affect is the body's main instrument for alerting consciousness to important homeostatic perturbations (for reviews, see Ekkekakis, 2003; Ekkekakis & Acevedo, 2006; Ekkekakis et al., 2005a). Within this framework, the apparently highly variable onset of increased oxygenation in the prefrontal cortex (Timinkul et al., 2008) could be related to individual differences in the cognitive control of the affective responses elicited by exercise (Ekkekakis, Hall, & Petruzzello, 2005b; Ekkekakis, Lind, Hall, & Petruzzello, 2007). As noted earlier, there is now a substantial literature examining the role of prefrontal cortical activity (using the hemodynamic BOLD signal of fMRI) in the cognitive control of negative affect (Ochsner & Gross, 2005, 2007). As these studies have demonstrated, increased activity in the prefrontal region appears to be closely coupled with an attenuation of activity in the amygdala. Based on neuroanatomical and neurophysiological data, the amygdala appears to be a central point of convergence for exercise-related interoceptive information and, presumably, a key structure in the coordination of the affective response to exercise (for a review of the relevant studies, see Ekkekakis & Acevedo, 2006). According to Davidson (2001, 2002; Davidson, Jackson, & Kalin, 2000), the prefrontal cortex exerts an inhibitory control over the amygdala during exposure to aversive stimuli, thus helping to regulate the negative affective responses that accompany aversive stimuli. Davidson et al. (2000) speculated that "in the absence of this normal inhibitory input, the amygdala remains unchecked and continues to remain activated" (p. 898).

Expanding upon this idea, research by Rosenkranz and Grace (2001) was based on the assumption that there is a balance between input to the basolateral amygdala from sensory (including somatosensory) afferents and input from the medial prefrontal cortex. According to these authors, this balance "may determine whether an amygdala-mediated affective response will be produced in the presence of an affective sensory stimulus" (p. 4090). Active inputs from the medial prefrontal cortex to the basolateral amygdala "may function to keep affective behaviors in check" (p. 4100). Therefore, as exercise intensity increases and begins to present an affective challenge (at different levels for different individuals, depending on their traits and situational appraisals), the cognitive mechanisms in the prefrontal cortex may become active, thus exerting an inhibitory control over the activity of the amygdala. Since blood flow (and oxygenation) follows neuronal function, the need to engage the prefrontal cortex to deal with the emerging displeasure of intensifying somatic cues could be the stimulus for the increase in prefrontal oxygenation during exercise that is found in NIRS studies.

On the other hand, there is a level of exercise intensity that represents what Dalsgaard and Secher (2007) called "an impending metabolic crisis" (p. 3338). At this level of intensity, possibly proximal to the respiratory compensation threshold (Bhambhani et al., 2007; Rupp & Perrey, 2008), the maintenance of a physiological steady state is impossible and, unless the work rate is reduced or exercise ceases, there is a real risk for collapse or irreparable damage. It is perhaps not a far-fetched teleological argument to suggest that a transient hypoactivation of the prefrontal cortex, allowing negative affective responses driven directly by interoceptive afferents to dominate conscious awareness, would be highly adaptive under these circumstances. This scenario seems entirely consistent with empirical observations of universally negative affective changes during the last stages of incremental exercise protocols and high correlations between affective responses and peripheral physiological indices of metabolic strain, such as blood lactate or the respiratory exchange ratio, during these final stages (Ekkekakis, 2003; Ekkekakis & Acevedo, 2006; Ekkekakis et al., 2005a).

The neurophysiological work of Rosenkranz and Grace (2001) has shown that dopamine levels in the basolateral amygdala play a key role in regulating the balance between the control of amygdala function from the prefrontal cortex or from sensory (including somatosensory) cues. According to these authors, increased dopamine levels can precipitate a "switch . . . from a state of suppression mediated by [medial prefrontal cortical] inputs to a state of sensory-driven affective behavior" (p. 4101). Interestingly, other research has established that dopamine levels in the basolateral amygdala increase significantly during stress (Inglis & Moghaddam, 1999). An exercise intensity near or above the respiratory compensation threshold would certainly qualify as "stress." Alternatively, impaired prefrontal inhibitory regulation of neurons in the basolateral amygdala and, consequently, uninhibited activation of the amygdala can "occur in cases of hypofrontality" (Rosenkranz & Grace, 2001, p. 4101), a transient or chronic decrease in the activity of the prefrontal cortex. The reduction in prefrontal oxygenation that is observed near the respiratory compensation threshold in NIRS studies (Bhambhani et al., 2007; Rupp & Perrey, 2008) could reflect this type of "switch" to a mode of affect induction that is unmediated by prefrontal control of the amygdala.

It should be noted here that a role for the prefrontal cortex in the regulation of the sense of fatigue has also been suggested in several neuroimaging studies of patients suffering from Parkinson's disease, multiple sclerosis, or chronic fatigue syndrome. In these studies, fatigue is considered the manifestation of a dysfunction in a network of cortical–subcortical interactions, which, in addition to the prefrontal cortex, includes the amygdala, the cingulate cortex, and the basal ganglia. In particular, consistent with the idea outlined here, lowered activity in the prefrontal cortex (associated with atrophy, reduced blood blow, or reduced glucose utilization) has been found to be linked to exacerbated reports of fatigue (for a review, see DeLuca, Genova, Capili, & Wylie, 2009).

These suggestions form a tentative explanatory framework that could be tested empirically in future research. Furthermore, it seems justified to suggest that future NIRS investigations in the context of exercise should at least incorporate an informed rationale for the number and location of the sites being sampled. The assumption that NIRS data collected from the forehead somehow reflect

global cerebral hemodynamics seems untenable in light of evidence from cognitive and affective neuroscience. It should be replaced by specific hypotheses about the functions that the underlying prefrontal cortex is theorized to serve in the context of a particular experimental paradigm. For researchers truly interested in the hemodynamics of the entire cortex, the transition to a multichannel setup capable of optical topographic studies will be necessary (e.g., Kohno et al., 2007; Miyai et al., 2001; Suzuki et al., 2004). For laboratories with the substantial budget required for such a system, the advantages are many (minimizing partial volume effects, not missing localized activation, accurate coregistration with individual anatomy, etc.).

Conclusion

NIRS certainly cannot compete with other imaging methods, especially fMRI, in spatial resolution. Moreover, except perhaps in neonates, NIRS cannot provide information on the function of subcortical structures. Nevertheless, the technology has improved considerably over the past several years, addressing such important challenges as the absolute quantification of O_2Hb and HHb and the attenuation of extracerebral influences. Furthermore, unlike other noninvasive techniques, NIRS measurements have high specificity and permit a relatively straightforward physiological interpretation. It is also worth noting that the cost of the technology (for systems with one, two, or four channels) is reasonable, making its widespread application in exercise psychology laboratories a realistic prospect. But perhaps most importantly, the unique advantage of NIRS is that, when proper care is taken to minimize movement artifacts, it can yield acceptable signal-to-noise ratios during exercise on most laboratory ergometers. This makes NIRS the most realistic option currently available for the assessment of human cortical activity during exercise. As the studies reviewed here illustrate, the application of NIRS during exercise is clearly feasible. The extant data offer, for the first time, intriguing insights into the workings of the prefrontal cortex during exercise. It is reasonable to suggest that integrating the psychological theories outlined here (and others) into future investigations creates very exciting possibilities for research on cognitive function and the cognitive control of affective responses to exercise.

References

Ainslie, P.N., Barach, A., Murrell, C., Hamlin, M., Hellemans, J., & Ogoh, S. (2007). Alterations in cerebral autoregulation and cerebral blood flow velocity during acute hypoxia: Rest and exercise. *The American Journal of Physiology, 292,* H976–H983.

Ainslie, P.N., Hamlin, M., Hellemans, J., Rasmussen, P., & Ogoh, S. (2008). Cerebral hypoperfusion during hypoxic exercise following two different hypoxic exposures: Independence from changes in dynamic autoregulation and reactivity. *The American Journal of Physiology, 295,* R1613–R1622.

Al-Rawi, P.G., Smielewski, P., & Kirkpatrick, P.J. (2001). Evaluation of a near-infrared spectrometer (NIRO 300) for the detection of intracranial oxygenation changes in the adult head. *Stroke, 32,* 2492–2500.

Alvarez, J.A., & Emory, E. (2006). Executive function and the frontal lobes: A meta-analytic review. *Neuropsychology Review, 16,* 17–42.

Apkarian, A.V., Bushnell, M.C., Treede, R-D., & Zubieta, J.K. (2005). Human brain mechanisms of pain perception and regulation in health and disease. *European Journal of Pain (London, England), 9,* 463–484.

Arridge, S.R., Cope, M., & Delpy, D.T. (1992). The theoretical basis for the determination of optical pathlengths in tissue: Temporal and frequency analysis. *Physics in Medicine and Biology, 37,* 1531–1560.

Arthurs, O.J., & Boniface, S. (2002). How well do we understand the neural origins of the fMRI BOLD signal? *Trends in Neurosciences, 25,* 27–31.

Bhambhani, Y.N. (2004). Muscle oxygenation trends during dynamic exercise measured by near infrared spectroscopy. *Canadian Journal of Applied Physiology, 29,* 504–523.

Bhambhani, Y., Malik, R., & Mookerjee, S. (2007). Cerebral oxygenation declines at exercise intensities above the respiratory compensation threshold. *Respiratory Physiology & Neurobiology, 156,* 196–202.

Boas, D.A., Dale, A.M., & Franceschini, M.A. (2004). Diffuse optical imaging of brain activation: Approaches to optimizing image sensitivity, resolution, and accuracy. *NeuroImage, 23,* S275–S288.

Boas, D.A., Gaudette, T., Strangman, G., Cheng, X., Marota, J.J.A., & Mandeville, J.B. (2001). The accuracy of near-infrared spectroscopy and imaging during focal changes in cerebral hemodynamics. *NeuroImage, 13,* 76–90.

Boecker, H., Henriksen, G., Sprenger, T., Miederer, I., Willoch, F., Valet, M., et al. (2008). Positron emission tomography ligand activation studies in the sports sciences: Measuring neurochemistry *in vivo. Methods (San Diego, Calif.), 45,* 307–318.

Boushel, R., Langberg, H., Olesen, J., Gonzales-Alonzo, J., Bülow, J., & Kjær, M. (2001). Monitoring tissue oxygen availability with near infrared spectroscopy (NIRS) in health and disease. *Scandinavian Journal of Medicine & Science in Sports, 11,* 213–222.

Buxton, R.B. (2002). Coupling between CBF and $CMRO_2$ during neuronal activity. In M. Tomita, I. Kanno, & E. Hamel (Eds.), *Brain activation and CBF control* (pp. 23–32). Amsterdam: Elsevier.

Buxton, R.B., & Frank, L.R. (1997). A model for the coupling between cerebral blood flow and oxygen metabolism during neural stimulation. *Journal of Cerebral Blood Flow and Metabolism, 17,* 64–72.

Buxton, R.B., Wong, E.C., & Frank, L.R. (1998). Dynamics of blood flow and oxygenation changes during brain activation: The balloon model. *Magnetic Resonance in Medicine, 39,* 855–864.

Chance, B., Leigh, J.S., Miyake, H., Smith, D.S., Nioka, S., Greenfeld, R., et al. (1988). Comparison of time-resolved and -unresolved measurements of deoxyhemoglobin in brain. *Proceedings of the National Academy of Sciences of the United States of America, 85,* 4971–4975.

Cope, M., & Delpy, D.T. (1988). System for long-term measurement of cerebral blood and tissue oxygenation on newborn infants by infra-red translumination. *Medical & Biological Engineering & Computing, 26,* 289–294.

Crabbe, J.B., & Dishman, R.K. (2004). Brain electrocortical activity during and after exercise: A quantitative synthesis. *Psychophysiology, 41,* 563–574.

Dalsgaard, M.K. (2006). Fuelling cerebral activity in exercising man. *Journal of Cerebral Blood Flow and Metabolism, 26,* 731–750.

Dalsgaard, M.K., & Secher, N.H. (2007). The brain at work: A cerebral metabolic manifestation of central fatigue? *Journal of Neuroscience Research, 85,* 3334–3339.

Davidson, R.J. (2001). The neural circuitry of emotion and affective style: Prefrontal cortex and amygdala contributions. *Social Sciences Information. Information Sur les Sciences Sociales, 40,* 11–37.

Davidson, R.J. (2002). Anxiety and affective style: Role of prefrontal cortex and amygdala. *Biological Psychiatry, 51,* 68–80.

Davidson, R.J. (2004a). Well-being and affective style: Neural substrates and biobehavioural correlates. *Philosophical Transactions of the Royal Society of London, 359 (Series B)*, 1395–1411.

Davidson, R.J. (2004b). What does the prefrontal cortex "do" in affect? Perspectives on frontal EEG asymmetry research. *Biological Psychology, 67,* 219–233.

Davidson, R.J., Jackson, D.C., & Kalin, N.H. (2000). Emotion, plasticity, context, and regulation: Perspectives from affective neuroscience. *Psychological Bulletin, 126,* 890–909.

Delpy, D.T., & Cope, M. (1997). Quantification in tissue near-infrared spectroscopy. *Philosophical transactions of the Royal Society of London, 352 (Series B)*, 649–659.

Delpy, D.T., Cope, M., van der Zee, P., Arridge, S., Wray, S., & Wyatt, J. (1988). Estimation of optical pathlength through tissue from direct time of flight measurement. *Physics in Medicine and Biology, 33,* 1433–1442.

DeLuca, J., Genova, H.M., Capili, E.J., & Wylie, G.R. (2009). Functional neuroimaging of fatigue. *Physical Medicine and Rehabilitation Clinics of North America, 20,* 325–337.

Dietrich, A. (2003). Functional neuroanatomy of altered states of consciousness: The transient hypofrontality hypothesis. *Consciousness and Cognition, 12,* 231–256.

Dietrich, A. (2006). Transient hypofrontality as a mechanism for the psychological effects of exercise. *Psychiatry Research, 145,* 79–83.

Dietrich, A., & Sparling, P.B. (2004). Endurance exercise selectively impairs prefrontal-dependent cognition. *Brain and Cognition, 55,* 516–524.

Dishman, R.K. (2005). The late arrival of exercise neuroscience. *International Journal of Sport and Exercise Psychology, 3,* 252–262.

Duncan, A., Meek, J.H., Clemence, M., Elwell, C.E., Tyszczuk, L., Cope, M., et al. (1995). Optical pathlength measurements on adult head, calf and forearm and the head of the newborn infant using phase resolved optical spectroscopy. *Physics in Medicine and Biology, 40,* 295–304.

Ekkekakis, P. (2003). Pleasure and displeasure from the body: Perspectives from exercise. *Cognition and Emotion, 17,* 213–239.

Ekkekakis, P., & Acevedo, E.O. (2006). Affective responses to acute exercise: Toward a psychobiological dose-response model. In E.O. Acevedo & P. Ekkekakis (Eds.), *Psychobiology of physical activity* (pp. 91–109). Champaign, IL: Human Kinetics.

Ekkekakis, P., Hall, E.E., & Petruzzello, S.J. (2005a). Variation and homogeneity in affective responses to physical activity of varying intensities: An alternative perspective on dose-response based on evolutionary considerations. *Journal of Sports Sciences, 23,* 477–500.

Ekkekakis, P., Hall, E.E., & Petruzzello, S.J. (2005b). Some like it vigorous: Individual differences in the preference for and tolerance of exercise intensity. *Journal of Sport & Exercise Psychology, 27,* 350–374.

Ekkekakis, P., Lind, E., Hall, E.E., & Petruzzello, S.J. (2007). Can self-reported tolerance of exercise intensity play a role in exercise testing? *Medicine and Science in Sports and Exercise, 39,* 1193–1199.

Essenpreis, M., Elwell, C.E., Cope, M., van der Zee, P., Arridge, S.R., & Delpy, D.T. (1993). Spectral dependence of temporal point spread functions in human tissues. *Applied Optics, 32,* 418–425.

Fallgatter, A.J., Müller, T.J., & Strik, W.K. (1998). Prefrontal hypooxygenation during language processing assessed with near-infrared spectroscopy. *Neuropsychobiology, 37,* 215–218.

Fantini, S., Franceschini, M.A., & Gratton, E. (1994). Semi-infinite-geometry boundary problem for light migration in highly scattering media: A frequency-domain study in the diffusion approximation. *Journal of the Optical Society of America, 11*(Series B), 2128–2138.

Fantini, S., Franceschini, M.A., Meier, J.S., Walker, S.A., Barbieri, B., & Gratton, E. (1995). Frequency-domain multichannel optical detector for noninvasive tissue spectroscopy and oximetry. *Optical Engineering, 34,* 32–42.

Fantini, S., Franceschini, M.A., Fishkin, J.B., Barbieri, B., & Gratton, E. (1994). Quantitative determination of the absorption spectra of chromophores in strongly scattering media: A light-emitting-diode based technique. *Applied Optics, 33,* 5204–5213.

Firbank, M., Okada, E., & Delpy, D.T. (1998). A theoretical study of the signal contribution of regions of the adult head to near-infrared spectroscopy studies of visual evoked responses. *NeuroImage, 8,* 69–78.

Fishkin, J.B., & Gratton, E. (1993). Propagation of photon-density waves in strongly scattering media containing an absorbing semi-infinite plane bounded by a straight edge. *Journal of the Optical Society of America, 10*(Series A), 127–140.

Fox, P.T., & Raichle, M.E. (1986). Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proceedings of the National Academy of Sciences of the United States of America, 83,* 1140–1144.

Fox, P.T., Raichle, M.E., Mintun, M.A., & Dence, C. (1988). Nonoxidative glucose consumption during focal physiologic neural activity. *Science, 241,* 462–464.

Fukui, Y., Ajichi, Y., & Okada, E. (2003). Monte-Carlo prediction of near-infrared light propagation in realistic adult and neonatal head models. *Applied Optics, 42,* 2881–2887.

Germon, T.J., Evans, P.D., Barnett, N.J., Wall, P., Manara, A.R., & Nelson, R.J. (1999). Cerebral near infrared spectroscopy: Emitter-detector separation must be increased. *British Journal of Anaesthesia, 82,* 831–837.

Germon, T.J., Evans, P.D., Manara, A.R., Barnett, N.J., Wall, P., & Nelson, R.J. (1998). Sensitivity of near-infrared spectroscopy to cerebral and extra-cerebral oxygenation changes in determined by emitter-detector separation. *Journal of Clinical Monitoring and Computing, 14,* 353–360.

Germon, T.J., Kane, N.M., Manara, A.R., & Nelson, R.J. (1994). Near-infrared spectroscopy in adults: Effects of extracranial ischaemia and intracranial hypoxia on estimation of cerebral oxygenation. *British Journal of Anaesthesia, 73,* 503–506.

González-Alonso, J., Dalsgaard, M.K., Osada, T., Volianitis, S., Dawson, E.A., Yoshiga, C.C., et al. (2004). Brain and central hemodynamics and oxygenation during maximal exercise in humans. *The Journal of Physiology, 557,* 331–342.

Gratton, G., Fabiani, M., Elbert, T., & Rockstroh, B. (2003). Seeing right through you: Applications of optical imaging to the study of the human brain. *Psychophysiology, 40,* 487–491.

Gratton, G., Fantini, S., Franceschini, M.A., Gratton, G., & Fabiani, M. (1997). Measurement of scattering and absorption changes in muscle and brain. *Philosophical Transactions of the Royal Society of London, 352*(Series B), 727–735.

Gratton, G., Maier, J.S., Fabiani, M., Mantulin, W.W., & Gratton, E. (1994). Feasibility of intracranial near-infrared optical scanning. *Psychophysiology, 31,* 211–215.

Gratton, E., Toronov, V., Wolf, U., Wolf, M., & Webb, A. (2005). Measurement of brain activity by near-infrared light. *Journal of Biomedical Optics, 10,* 011008.

Hemelt, M.W., & Kang, K.A. (1999). Determination of a biological absorber depth utilizing multiple source-detector separations and multiple frequency values of near-infrared time-resolved spectroscopy. *Biotechnology Progress, 15,* 622–629.

Hiraoka, M., Firbank, M., Essenpreis, M., Cope, M., Arridge, S.R., van der Zee, P., et al. (1993). A Monte Carlo investigation of optical pathlength in inhomogeneous tissue and its application to near-infrared spectroscopy. *Physics in Medicine and Biology, 38,* 1859–1876.

Hoshi, Y. (2003). Functional near-infrared optical imaging: Utility and limitations in human brain mapping. *Psychophysiology, 40,* 511–520.

Hoshi, Y. (2005). Functional near-infrared spectroscopy: Potential and limitations in neuroimaging studies. *International Review of Neurobiology, 66,* 237–266.

Hoshi, Y., Kobayashi, N., & Tamura, M. (2001). Interpretation of near-infrared spectroscopy signals: A study with a newly developed perfused rat brain model. *Journal of Applied Physiology, 90,* 1657–1662.

Hueber, D.M., Franceschini, M.A., Ma, H.Y., Zhang, Q., Ballesteros, J.R., Fantini, S., et al. (2001). Non-invasive and quantitative near-infrared haemoglobin spectrometry in the piglet brain during hypoxic stress, using a frequency-domain multidistance instrument. *Physics in Medicine and Biology, 46,* 41–62.

Huppert, T.J., Hoge, R.D., Diamond, S.G., Franceschini, M.A., & Boas, D.A. (2006). A temporal comparison of BOLD, ASL, and NIRS hemodynamic responses to motor stimuli in adult humans. *NeuroImage, 29,* 368–382.

Ide, K., Horn, A., & Secher, N.H. (1999). Cerebral metabolic response to submaximal exercise. *Journal of Applied Physiology, 87,* 1604–1608.

Ide, K., & Secher, N.H. (2000). Cerebral blood flow and metabolism during exercise. *Progress in Neurobiology, 61,* 397–414.

Imray, C.H.E., Myers, S.D., Pattinson, K.T.S., Bradwell, A.R., Chan, C.W., Harris, S., et al. (2005). Effect of exercise on cerebral perfusion in humans at high altitude. *Journal of Applied Physiology, 99,* 699–706.

Inglis, F.M., & Moghaddam, B. (1999). Dopaminergic innervation of the amygdala is highly responsive to stress. *Journal of Neurochemistry, 72,* 1088–1094.

Izzetoglu, M., Devaraj, A., Bunce, S., & Onaral, B. (2005). Motion artifact cancellation in NIR spectroscopy using Wiener filtering. *IEEE Transactions on Bio-Medical Engineering, 52,* 934–938.

Jensen, G., Nielsen, H.B., Ide, K., Madsen, P.L., Svendsen, L.B., Svendsen, U.G., et al. (2002). Cerebral oxygenation during exercise in patients with terminal lung disease. *Chest, 122,* 445–450.

Jöbsis, F.F. (1977). Non-invasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science, 198,* 1264–1267.

Kayser, B. (2003). Exercise starts and ends in the brain. *European Journal of Applied Physiology, 90,* 411–419.

Kirkpatrick, P.J., Smielewski, P., Whitfield, P.C., Czosnyka, M., Menon, D., & Pickard, J.D. (1995). A observational study of near-infrared spectroscopy during carotid endarterectomy. *Journal of Neurosurgery, 82,* 756–763.

Kleinschmidt, A., Obrig, H., Requardt, M., Merboldt, K.D., Dirnagl, U., Villringer, A., et al. (1996). Simultaneous recording of cerebral blood oxygenation changes during human brain activation by magnetic resonance imaging and near-infrared spectroscopy. *Journal of Cerebral Blood Flow and Metabolism, 16,* 817–826.

Kohl, M., Nolte, C., Heekeren, H.R., Horst, S., Scholz, U., Obrig, H., et al. (1998). Determination of the wavelength dependence of the differential pathlength factor from near-infrared pulse signals. *Physics in Medicine and Biology, 43,* 1771–1782.

Kohno, S., Miyai, I., Seiyama, A., Oda, I., Ishikawa, A., Tsuneishi, S., et al. (2007). Removal of the skin blood flow artifact in functional near-infrared spectroscopic imaging data through independent component analysis. *Journal of Biomedical Optics, 12,* 62111.

Kohri, S., Hoshi, Y., Tamura, M., Kato, C., Kuge, Y., & Tamaki, N. (2002). Quantitative evaluation of the relative contribution ratio of cerebral tissue to near-infrared signals in the adult human head: A preliminary study. *Physiological Measurement, 23,* 301–312.

Koike, A., Hoshimoto, M., Nagayama, O., Tajima, A., Kubozono, T., Oikawa, K., et al. (2004). Cerebral oxygenation during exercise and exercise recovery in patients with idiopathic dilated cardiomyopathy. *The American Journal of Cardiology, 94,* 821–824.

Koike, A., Hoshimoto, M., Tajima, A., Nagayama, O., Yamaguchi, K., Goda, A., et al. (2006). Critical level of cerebral oxygenation during exercise in patients with left ventricular dysfunction. *Circulation Journal, 70,* 1457–1461.

Koike, A., Itoh, H., Oohara, R., Hoshimoto, M., Tajima, A., Aizawa, T., et al. (2004). Cerebral oxygenation during exercise in cardiac patients. *Chest, 125,* 182–190.

Koike, A., Nagayama, O., Goda, A., Hoshimoto, M., Yamaguchi, K., Tajima, A., et al. (2007). Effects of supplemental O_2 inhalation on cerebral oxygenation during exercise in patients with left ventricular dysfunction. *Circulation Journal, 71,* 1418–1423.

Lakowicz, J.R., & Berndt, K. (1990). Frequency-domain measurements of photon migration in tissues. *Chemical Physics Letters, 166,* 246–252.

Lang, P.J. (1994). The varieties of emotional experience: A meditation on James-Lange theory. *Psychological Review, 101,* 211–221.

Lewis, M.J. (2003). Biomagnetism: A new tool in sport and exercise science. *Journal of Sports Sciences, 21,* 793–802.

Logothetis, N.K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation if the basis of the fMRI signal. *Nature, 412,* 150–157.

MacIntosh, B.J., Klassen, L.M., & Menon, R.S. (2003). Transient hemodynamics during a breath hold challenge in a two part functional imaging study with simultaneous near-infrared spectroscopy in adult humans. *NeuroImage, 20,* 1246–1252.

Madsen, P.L., & Secher, N.H. (1999). Near-infrared oximetry of the brain. *Progress in Neurobiology, 58,* 541–560.

Marshall, H.C., Hamlin, M.J., Hellemans, J., Murrell, C., Beattie, N., Perry, T., et al. (2008). Effects of intermittent hypoxia on SaO_2, cerebral and muscle oxygenation during maximal exercise in athletes with exercise-induced hypoxemia. *European Journal of Applied Physiology, 104,* 383–393.

Mason, P.F., Dyson, E.H., Sellars, V., & Beard, J.D. (1994). The assessment of cerebral oxygenation during carotid endarterectomy utilising near infrared spectroscopy. *European Journal of Vascular Surgery, 8,* 590–594.

Mehagnoul-Schipper, D.J., van der Kallen, B.F.W., Colier, W.N.J.M., van der Sluijs, M.C., van Erning, L.J.T.O., Thijssen, H.O.M., et al. (2002). Simultaneous measurements of cerebral oxygenation changes during brain activation by near-infrared spectroscopy and functional magnetic resonance imaging in healthy young and elderly subjects. *Human Brain Mapping, 16,* 14–23.

Mehta, J.P., Verber, M.D., Wieser, J.A., Schmit, B.D., & Schindler-Ivens, S.M. (2009). A novel technique for examining human brain activity associated with pedaling using fMRI. *Journal of Neuroscience Methods, 179,* 230–239.

Mintun, M.A., Lundstrom, B.N., Snyder, A.Z., Vlassenko, A.G., Shulman, G.L., & Raichle, M.E. (2001). Blood flow and oxygen delivery to human brain during functional activity: Theoretical modeling and experimental data. *Proceedings of the National Academy of Sciences of the United States of America, 98,* 6859–6864.

Miyai, I., Tanabe, H.C., Sase, I., Eda, H., Oda, I., Konishi, I., et al. (2001). Cortical mapping of gait in humans: A near-infrared spectroscopic topography study. *NeuroImage, 14,* 1186–1192.

Morinaga, K., Akiyoshi, J., Matsushita, H., Ichioka, S., Tanaka, Y., Tsuru, J., et al. (2007). Anticipatory anxiety-induced changes in human lateral prefrontal cortex activity. *Biological Psychology, 74,* 34–38.

Nagayama, O., Koike, A., Hoshimoto, M., Yamaguchi, K., Tajima, A., Goda, A., et al. (2007). Influence of cerebrovascular arteriosclerosis on cerebral oxygenation during exercise. *Circulation Journal, 71,* 782–787.

Neary, J.P. (2004). Application of near infrared spectroscopy to exercise sports science. *Canadian Journal of Applied Physiology, 29,* 488–503.

Neary, J.P., Roberts, A.D.W., Leavins, N., Harrison, M.F., Croll, J.C., & Sexsmith, J.R. (2008). Prefrontal cortex oxygenation during incremental exercise in chronic fatigue syndrome. *Clinical Physiology and Functional Imaging, 28,* 364–372.

Nee, D.E., Wager, T.D., & Jonides, J. (2007). Interference resolution: Insights from a meta-analysis of neuroimaging tasks. *Cognitive, Affective & Behavioral Neuroscience, 7,* 1–17.

Nielsen, H.B., Boesen, M., & Secher, N.H. (2001). Near-infrared spectroscopy determined brain and muscle oxygenation during exercise with normal and resistive breathing. *Acta Physiologica Scandinavica, 171,* 63–70.

Nielsen, H.B., Boushel, R., Madsen, P., & Secher, N.H. (1999). Cerebral desaturation during exercise reversed by O_2 supplementation. *The American Journal of Physiology, 277,* H1045–H1052.

Nielsen, H.B., Secher, N.H., Clemmesen, O., & Ott, P. (2005). Maintained cerebral and skeletal muscle oxygenation during maximal exercise in patients with liver cirrhosis. *Journal of Hepatology, 43,* 266–271.

Noakes, T.D., Peltonen, J.E., & Rusko, H.K. (2001). Evidence that a central governor regulates exercise performance during acute hypoxia and hyperoxia. *The Journal of Experimental Biology, 204,* 3225–3234.

Nybo, L., & Rasmussen, P. (2007). Inadequate cerebral oxygen delivery and central fatigue during strenuous exercise. *Exercise and Sport Sciences Reviews, 35,* 110–118.

Nybo, L., & Secher, N.H. (2004). Cerebral perturbations provoked by prolonged exercise. *Progress in Neurobiology, 72,* 223–261.

Obrig, H., & Villringer, A. (2003). Beyond the visible: Imaging the human brain with light. *Journal of Cerebral Blood Flow and Metabolism, 23,* 1–18.

Obrig, H., Wenzel, R., Kohl, M., Horst, S., Wobst, P., Steinbrink, J., et al. (2000). Near-infrared spectroscopy: Does it function in functional activation studies of the adult brain? *International Journal of Psychophysiology, 35,* 125–142.

Ochsner, K.N., & Gross, J.J. (2005). The cognitive control of emotion. *Trends in Cognitive Sciences, 9,* 242–249.

Ochsner, K.N., & Gross, J.J. (2007). The neural architecture of emotion regulation. In J.J. Gross (Ed.), *Handbook of emotion regulation* (pp. 87–109). New York: Guilford.

Ogawa, S., Lee, T.M., Kay, A.R., & Tank, D.W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences of the United States of America, 87,* 9868–9872.

Ohmae, E., Ouchi, Y., Oda, M., Suzuki, T., Nobesawa, S., Kanno, T., et al. (2006). Cerebral hemodynamics evaluation by near-infrared time-resolved spectroscopy: Correlation with simultaneous positron emission tomography measurements. *NeuroImage, 29,* 697–705.

Okada, E., Firbank, M., Schweiger, M., Arridge, S.R., Cope, M., & Delpy, D.T. (1997). Theoretical and experimental investigation of near-infrared light propagation in a model of the adult head. *Applied Optics, 36,* 21–31.

Okamoto, M., Dan, H., Shimizu, K., Takeo, K., Amita, T., Oda, I., et al. (2004). Multimodal assessment of cortical activation during apple peeling by NIRS and fMRI. *NeuroImage, 21,* 1275–1288.

Owen-Reece, H., Elwell, C.E., Wyatt, J.S., & Delpy, D.T. (1996). The effect of scalp ischaemia on measurement of cerebral blood volume by near-infrared spectroscopy. *Physiological Measurement, 17,* 279–286.

Owen-Reece, H., Smith, M., Elwell, C.E., & Goldstone, J.C. (1999). Near-infrared spectroscopy. *British Journal of Anaesthesia, 82,* 418–426.

Patterson, M.S., Chance, B., & Wilson, B.C. (1989). Time resolved reflectance and transmittance for the non-invasive measurement of tissue optical properties. *Applied Optics, 28,* 2331–2336.

Pauling, L., & Coryell, C.D. (1936). The magnetic properties and structure of hemoglobin, oxyhemoglobin and carbonmonoxyhemoglobin. *Proceedings of the National Academy of Sciences of the United States of America, 22,* 210–216.

Pereira, M.I.R., Gomes, P.S.C., & Bhambhani, Y.N. (2007). A brief review of the use of near infrared spectroscopy with particular interest in resistance exercise. *Sports Medicine (Auckland, N.Z.), 37,* 615–624.

Perrey, S. (2008). Non-invasive NIR spectroscopy of human brain function during exercise. *Methods (San Diego, Calif.), 45,* 289–299.

Petruzzello, S.J., Ekkekakis, P., & Hall, E.E. (2006). Physical activity, affect, and electroencephalogram studies. In E.O. Acevedo & P. Ekkekakis (Eds.), *Psychobiology of physical activity* (pp. 111–128). Champaign, IL: Human Kinetics.

Petruzzello, S.J., Hall, E.E., & Ekkekakis, P. (2001). Regional brain activation as a biological marker of affective responsivity to acute exercise: Influence of fitness. *Psychophysiology, 38,* 99–106.

Phan, K.L., Wager, T., Taylor, S.F., & Liberzon, I. (2002). Functional neuroanatomy of emotion: A meta-analysis of emotion activation studies in PET and fMRI. *NeuroImage, 16,* 331–348.

Powers, W.J., Hirsch, I.B., & Cryer, P.E. (1996). Effect of stepped hypoglycemia on regional cerebral blood flow response to physiological brain activation. *The American Journal of Physiology, 270,* H554–H559.

Quaresima, V., Lepanto, R., & Ferrari, M. (2003). The use of near infrared spectroscopy in sports medicine. *Journal of Sports, Medicine, and Physical Fitness, 43,* 1–13.

Raichle, M.E. (2001). Bold insights. *Nature, 412,* 128–130.

Raichle, M. (2002). The circulatory and metabolic correlates of functional activity. In M. Tomita, I. Kanno, & E. Hamel (Eds.), *Brain activation and CBF control* (pp. 15–20). Amsterdam: Elsevier.

Raichle, M.E., & Mintun, M.A. (2006). Brain work and brain imaging. *Annual Review of Neuroscience, 29,* 449–476.

Rao, R.P., Danduran, M.J., Frommelt, P.C., Ghanayem, N.S., Berger, S., Simpson, P.M., et al. (2009).Measurement of regional tissue bed venous weighted oximetric trends during exercise by near infrared spectroscopy. *Pediatric Cardiology, 30, 465–471.*

Rolfe, P. (2000). In vivo near-infrared spectroscopy. *Annual Review of Biomedical Engineering, 2,* 715–754.

Rosenkranz, J.A., & Grace, A.A. (2001). Dopamine attenuates prefrontal cortical suppression of sensory inputs to the basolateral amygdala of rats. *The Journal of Neuroscience, 21,* 4090–4103.

Rostrup, E., Law, I., Pott, F., Ide, K., & Knudsen, G.M. (2002). Cerebral hemodynamics measured with simultaneous PET and near-infrared spectroscopy in humans. *Brain Research, 954,* 183–193.

Rupp, T., & Perrey, S. (2008). Prefrontal cortex oxygenation and neuromuscular responses to exhaustive exercise. *European Journal of Applied Physiology, 102,* 153–163.

Saito, S., Nishihara, F., Takazawa, T., Kanai, M., Aso, S., Shiga, T., et al. (1999). Exercise-induced cerebral deoxygenation among untrained trekkers at moderate altitudes. *Archives of Environmental Health, 54,* 271–276.

Sassaroli, A., Frederick, B.B., Tong, Y., Renshaw, P.F., & Fantini, S. (2006). Spatially weighted BOLD signal for comparison of functional magnetic resonance imaging and near-infrared imaging of the brain. *NeuroImage, 33,* 505–514.

Sato, H., Kiguchi, A., Kawaguchi, F., & Maki, A. (2004). Practicality of wavelength selection to improve signal-to-noise ratio in near-infrared spectroscopy. *NeuroImage, 21,* 1554–1562.

Sato, H., Tanaka, N., Uchida, M., Hirabayashi, Y., Kanai, M., Ashida, T., et al. (2006). Wavelet analysis for detecting body-movement artifacts in optical topography signals. *NeuroImage, 33,* 580–587.

Seifert, T., Rasmussen, P., Secher, N.H., & Nielsen, H.B. (2009).Cerebral oxygenation decreases during exercise in humans with beta-adrenergic blockade. *Acta Physiologica, 196,* 295–302.

Shibuya, K., Tanaka, J., Kuboyama, N., Murai, S., & Ogaki, T. (2004). Cerebral cortex activity during supramaximal exhaustive exercise. *Journal of Sports, Medicine, and Physical Fitness, 44,* 215–219.

Shibuya, K., Tanaka, J., Kuboyama, N., & Ogaki, T. (2004). Cerebral oxygenation during intermittent supramaximal exercise. *Respiratory Physiology & Neurobiology, 140,* 165–172.

Steinbrink, J., Villringer, A., Kempf, F., Haux, D., Boden, S., & Obrig, H. (2006). Illuminating the BOLD signal: Combined fMRI-fNIRS studies. *Magnetic Resonance Imaging, 24,* 495–505.

Steinbrink, J., Wabnitz, H., Obrig, H., Villringer, A., & Rinneberg, H. (2001). Determining changes in NIR absorption using a layered model of the human head. *Physics in Medicine and Biology, 46,* 879–896.

Strangman, G., Boas, D.A., & Sutton, J.P. (2002). Non-invasive neuroimaging using near-infrared light. *Biological Psychiatry, 52,* 679–693.

Strangman, G., Culver, J.P., Thompson, J.H., & Boas, D.A. (2002). A quantitative comparison of simultaneous BOLD fMRI and NIRS recordings during functional brain activation. *NeuroImage, 17,* 719–731.

Strangman, G., Franceschini, M.A., & Boas, D.A. (2003). Factors affecting the accuracy of near-infrared spectroscopy concentration calculations for focal changes in oxygenation parameters. *NeuroImage, 18,* 865–879.

Subudhi, A.W., Dimmen, A.C., & Roach, R.C. (2007). Effects of acute hypoxia on cerebral and muscle oxygenation during incremental exercise. *Journal of Applied Physiology, 103,* 177–183.

Subudhi, A.W., Lorenz, M.C., Fulco, C.S., & Roach, R.C. (2008). Cerebrovascular responses to incremental exercise during hypobaric hypoxia: Effect of oxygenation on maximal performance. *The American Journal of Physiology, 294,* H164–H171.

Subudhi, A.W., Miramon, B.R., Granger, M.E., & Roach, R.C. (2009). Frontal and motor cortex oxygenation during maximal exercise in normoxia and hypoxia. *Journal of Applied Physiology, 106,* 1153–1158.

Suzuki, M., Miyai, I., Ono, T., Oda, I., Konishi, I., Kochiyama, T., et al. (2004). Prefrontal and premotor cortices are involved in adapting walking and running speed on the treadmill: An optical topography study. *NeuroImage, 23,* 1020–1026.

Tashiro, M., Itoh, M., Fujimoto, T., Masud, M.M., Watanuki, S., & Yanai, K. (2008). Application of positron emission tomography to neuroimaging in sports sciences. *Methods (San Diego, Calif.), 45,* 300–306.

Thompson, T., Steffert, T., Ros, T., Leach, J., & Gruzelier, J. (2008). EEG applications for sport and performance. *Methods (San Diego, Calif.), 45,* 279–288.

Timinkul, A., Kato, M., Omori, T., Deocaris, C.C., Ito, A., Kizuka, T., et al. (2008). Enhancing effect of cerebral blood volume by mild exercise in healthy young men: A near-infrared spectroscopy study. *Neuroscience Research, 61,* 242–248.

Toronov, V., Walker, S., Gupta, R., Choi, J.H., Gratton, E., Hueber, D., et al. (2003). The roles of changes in deoxyhemoglobin concentration and regional cerebral blood volume in the fMRI BOLD signal. *NeuroImage, 19,* 1521–1531.

Toronov, V., Webb, A., Choi, J.H., Wolf, M., Michalos, A., Gratton, E., et al. (2001). Investigation of human brain hemodynamics by simultaneous near-infrared spectroscopy and functional magnetic resonance imaging. *Medical Physics, 28,* 521–527.

Toronov, V., Webb, A., Choi, J.H., Wolf, M., Safanova, L., Wolf, U., et al. (2001). Study of local cerebral hemodynamics by frequency-domain near-infrared spectroscopy and correlation with simultaneously acquired functional magnetic resonance imaging. *Optics Express, 9,* 417–427.

Ugurbil, K., Toth, L., & Kim, D-S. (2003). How accurate is magnetic resonance imaging of brain function? *Trends in Neurosciences, 26,* 108–114.

Uludag, K., Kohl, M., Steinbrink, J., Obrig, H., & Villringer, A. (2002). Cross talk in the Lambert-Beer calculation for near-infrared wavelengths estimated by Monte Carlo simulations. *Journal of Biomedical Optics, 7,* 51–59.

Uludag, K., Steinbrink, J., Villringer, A., & Obrig, H. (2004). Separability and cross talk: Optimizing dual wavelength combinations for near-infrared spectroscopy of the adult head. *NeuroImage, 22,* 583–589.

Van der Zee, P., Cope, M., Arridge, S.R., Essenpreis, M., Potter, L.A., Edwards, A.D., et al. (1992). Experimentally measured optical pathlengths for the adult head, calf, and forearm and the head of the newborn infant as a function of inter optode spacing. *Advances in Experimental Medicine and Biology, 316,* 143–153.

Villringer, A., & Chance, B. (1997). Non-invasive optical spectroscopy and imaging of human brain function. *Trends in Neurosciences, 20,* 435–442.

Villringer, A., & Dirnagl, U. (1995). Coupling of brain activity and cerebral blood flow: Basis of functional neuroimaging. *Cerebrovascular and Brain Metabolism Reviews, 7,* 240–276.

Villringer, K., Minoshima, S., Hock, C., Obrig, H., Ziegler, S., Dirnagl, U., et al. (1997). Assessment of local brain activation: A simultaneous PET and near-infrared spectroscopy study. *Advances in Experimental Medicine and Biology, 413,* 149–153.

Villringer, A., & Obrig, H. (2002). Near-infrared spectroscopy and imaging. In A.W. Toga & J.C. Mazziotta (Eds.), *Brain mapping: The methods* (2nd ed., pp. 141–158). Amsterdam: Academic.

Williamson, J.W. (2006). Brain activation during physical activity. In E.O. Acevedo & P. Ekkekakis (Eds.), *Psychobiology of physical activity* (pp. 29–44). Champaign, IL: Human Kinetics.

Wray, S., Cope, M., Delpy, D.T., Wyatt, J.S., & Reynolds, E.O.R. (1988). Characterization of the near infrared absorption spectra of cytochrome $\alpha\alpha_3$ and haemoblobin for the non-invasive monitoring of cerebral oxygenation. *Biochimica et Biophysica Acta, 933,* 184–192.

Yamashita, Y., Maki, A., & Koizumi, H. (2001). Wavelength dependence of the precision of noninvasive optical measurement of oxy-, deoxy-, and total-hemoglobin concentration. *Medical Physics, 28,* 1108–1114.

Yoshitani, K., Kawaguchi, M., Miura, N., Okuno, T., Kanoda, T., Ohnishi, Y., et al. (2007). Effects of hemoglobin concentration, skull thickness, and the area of the cerebrospinal fluid layer on near-infrared spectroscopy measurements. *Anesthesiology, 106,* 458–462.

Young, A.E.R., Germon, T.J., Barnett, N.J., Manara, A.R., & Nelson, R.J. (2000). Behaviour of near-infrared light in the adult human head: Implications for clinical near-infrared spectroscopy. *British Journal of Anaesthesia, 84,* 38–42.

Zhao, H., Tanikawa, Y., Gao, F., Onodera, Y., Sassaroli, A., Tanaka, K., et al. (2002). Maps of optical differential pathlength factor of human adult forehead, somatosensory motor and occipital regions at multi-wavelengths in NIR. *Physics in Medicine and Biology, 47,* 2075–2093.

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