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Effects of incremental exercise on cerebral oxygenation measured by near-infrared spectroscopy: A systematic review

Cherie R. Rooks, Nathaniel J. Thom, Kevin K. McCully, Rod K. Dishman *

Department of Kinesiology, University of Georgia, 330 River Road, Athens, GA 30602-6554, United States

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ABSTRACT

We conducted a systematic review and meta-regression analysis to quantify effects of exercise on brain hemodynamics measured by near-infrared spectroscopy (NIRS). The results indicate that acute incremental exercise (categorized relative to aerobic capacity (VO_2peak) as low – <30% VO_2peak; moderate – ≥30% VO_2peak to <60% VO_2peak; hard – ≥60% VO_2peak to <VO_2peak; and very hard – ≥VO_2peak intensities) performed by 291 healthy people in 21 studies is accompanied by moderate-to-large increases (mean effect, $dz \pm 95\%$ CI) in the prefrontal cortex of oxygenated hemoglobin (O_2Hb) or other measures of oxygen level (O_2Hbdiff) or saturation (SCO_2) (0.92 ± 0.67, 1.17), deoxygenated hemoglobin (dHb) (0.87 ± 0.56, 1.19), and blood volume estimated by total hemoglobin (tHb) (1.21 ± 0.84, 1.59). After peaking at hard intensities, cerebral oxygen levels dropped during very hard intensities. People who were aerobically trained attained higher levels of cortical oxygen, dHb, and tHb than untrained people during very hard intensities. Among untrained people, a marked drop in oxygen levels and a small increase in dHb at very hard intensities accompanied declines in tHb, implying reduced blood flow. In 6 studies of 222 patients with heart or lung conditions, oxygenation and dHb were lowered or unchanged during exercise compared to baseline. In conclusion, prefrontal oxygenation measured with NIRS in healthy people showed a quadratic response to incremental exercise, rising between moderate and hard intensities, then falling at very hard intensities. Training status influenced the responses. While methodological improvements in measures of brain oxygen are forthcoming, these results extend the evidence relevant to existing models of central limitations to maximal exercise.

Contents

Abbreviations: SPECT, single photon emission computerized tomography; fMRI, functional magnetic resonance imaging; NIRS, near-infrared spectroscopy; O_2Hb, oxyhemoglobin; dHb, de-oxygenated hemoglobin; tHb, total hemoglobin; TOI, tissue oxygenation index; O_2Hbdiff, hemoglobin difference; SCO_2, cerebral oxygen saturation; $PaCO_2$, partial pressure of carbon dioxide; $PETCO_2$, partial pressure of end-tidal CO_2; VO_2peak, the highest measured oxygen uptake during incremental exercise; VO_2max, a plateau in oxygen uptake despite increasing exercise intensity.

* Corresponding author. Tel.: +1 706 542 9840; fax: +1 706 542 3148.
E-mail address: rdishman@uga.edu (R.K. Dishman).

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1. Introduction

Knowledge of how the central nervous system (CNS) influences motor neurons to limit neuromuscular performance is nascent (Duchateau and Enoka, 2002; Gandevia, 2001; Noakes et al., 2005; Nybo and Secher, 2004; Secher et al., 2008). It is accepted that motor command and its corollaries exist at multiple levels in the CNS to sustain homeostatic functions during exercise. Likewise, several metabolic and neurochemical pathways between skeletal muscles, the spinal cord, and the brain suggest ways by which exercise might influence the CNS (Dishman et al., 2006).

Three lines of research on the brain during exercise have focused on cerebral hemodynamic responses. One line has described brain blood flow, metabolism, and oxygenation during exercise under neutral ambient conditions or hostile conditions such as heat and hypoxia (Ide and Secher, 2000; Nybo and Secher, 2004). The other two lines have evaluated the role that the brain plays in regulating cardiovascular responses during exercise (Williamson et al., 2006) and maximal effort and fatigue (Dalsgaard and Secher, 2007; Noakes et al., 2005). In addition, other investigators have been interested in these lines of research in order to better understand the neural correlates of cognitive and affective responses that occur both during and after exercise (Dietrich, 2006).

Several methods have been used to evaluate brain hemodynamic responses during exercise since an increase in cerebral blood flow during muscular exercise was described more than 100 years ago (Roy and Sherrington, 1890). Initially, studies measured arterial-venous differences in nitrous oxide concentrations using the Kety–Schmidt method to determine blood flow changes during exercise (Folkow and Neil, 1971). Those studies mostly reported that global cerebral blood flow remained stable during exercise (e.g., Scheinberg et al., 1954; Zobl et al., 1965), leading to the long-standing view that the brain auto-regulates blood flow during exercise. By contrast, studies using transcranial Doppler ultrasonography (which cannot distinguish between changes in regional and global cerebral blood flow), as well as direct measurements of blood flow through the internal carotid artery, suggested that brain blood flow increases during exercise (Ide et al., 1998; Jorgensen et al., 1992a, 1992b; Linkis et al., 1995; Samnegard and Carlens, 1975), but not at a rate proportional to increased cardiac output (Gonzalez-Alonso and Calbet, 2003; Gonzalez-Alonso et al., 2004; Rowell, 1974). Because mean arterial pressure during incremental exercise typically remains within the range of cerebral auto-regulation, it is now generally accepted that global brain blood flow is not altered during low-to-hard exercise in healthy humans (Ide and Secher, 2000), but may decline during high-intensity exercise (Ogoh and Ainslie, 2009a, 2009b).

Less is known about regional distribution of brain blood flow during moderate-to-exhaustive exercise. The ^{133}Xenon clearance method permits the detection of regional changes in cerebral blood flow, but it requires a stationary head and a long period (~10 min) of near steady state recording, which each preclude the detection of increased blood flow at high or maximal intensities (e.g., above ~50–60% aerobic capacity) in most people (Thomas et al., 1989). Use of radiolabeled microspheres in miniature swine suggests that increased flow is distributed to the cerebellum (Foreman et al., 1976) and sub-cortical, but not cortical, sensory and motor control regions (Delp et al., 2001) during high-intensity exercise. Studies using single photon emission computerized tomography (SPECT) identified increases in regional cerebral blood flow in the thalamus and several cortical and sub-cortical regions (insular cortex, anterior cingulate, medial prefrontal), implicating them in regulation by central command of cardiovascular responses during leg cycling and handgrip exercise (Williamson et al., 2006). Because tracer uptake by the brain is proportional to brain blood flow, SPECT allows post hoc estimates of change in blood flow that occurred during dynamic exercise. However, SPECT does not provide direct measures of brain oxygenation.

Functional magnetic resonance imaging (fMRI) and near-infrared spectroscopy (NIRS) each provide a measure of cerebral oxygenation, as well as other hemodynamic measures (Huppert et al., 2006). However, fMRI requires that the participant remain virtually motionless during data acquisition, which precludes using this technique during dynamic exercise. NIRS, however, has been used extensively to evaluate hemodynamic changes during dynamic exercise in skeletal muscle (Hamaoka et al., 2007; McCully and Hamaoka, 2000) and more recently in brain (Perrey, 2008). The advantage of NIRS over the other methods mentioned is that it provides direct, real-time measures of oxygenation in cortical tissue with acceptable spatial resolution (~1 cm) and is not as sensitive to movement artifact as other measures.

NIRS technology passes near-infrared (700–1000 nm) light through tissue, where it is either absorbed by chromophores such as oxyhemoglobin (O_2Hb), deoxyhemoglobin (dHb), or cytochrome oxidase or is scattered within the tissue. By measuring the returned, scattered light at specific wavelengths, the relative level of O_2Hb and dHb absorbed in the underlying tissue can be determined (Ferrari et al., 2004). The use of NIRS to evaluate hemodynamic changes in the brain during exercise has increased as NIRS systems have become more available (Perrey, 2008; Wolf et al., 2007).

As far as we know, no quantitative analysis has been performed on the cumulative evidence from studies that used NIRS to measure brain hemodynamic responses during exercise. Quantifying the effects of exercise on cerebral blood volume and oxygenation could guide future studies of brain mechanisms that regulate performance during exercise by testing for potential moderators (i.e., effect modifiers) of variation in effects during exercise. The effect size estimates (i.e., standardized change scores) that result from a quantitative synthesis can also inform choices about the sample sizes needed to provide statistically powerful tests of hypotheses about key influences on brain hemodynamics during exercise.

We report here a systematic review and meta-regression analysis of studies that used NIRS to measure changes in brain

oxygenation, deoxygenation, and blood volume during incremental exercise performed in neutral ambient conditions by healthy people and patients. We limited the review to exercise types and intensities sufficient to increase cardiac output and systemic blood pressure which, thus, might challenge homeostatic regulation of peripheral and central blood circulation and neural metabolic activity in the brain. We evaluated potential moderating effects of features of the exercise stimulus, characteristics of people, and differences in NIRS methodology on variation in the observed effects. We focused on three main questions: (a) What are the direction and size of changes in brain oxygenation, deoxygenation, and total blood volume that accompany the increasing homeostatic load on peripheral organ systems during incremental exercise? (b) Do brain hemodynamic responses during varying intensities of exercise differ between people of different training history, ages or health status, which each affect the ability to exert a maximal effort? (c) Is variation in results across studies explainable by differences in NIRS methodology such as the number of detectors (e.g., brain region and optode distance)?

2. Methods

2.1. Literature search

Studies were located using the following online search engines: *Web of Science*, *Pubmed*, and *Google Scholar* with the terms: "near-infrared spectroscopy", "NIRS", "brain", "oxygenation", "blood flow", "exercise", "physical activity", "cerebral tissue oxygenation", and "cerebral oxygenation". The reference lists of the articles found during the aforementioned search were reviewed as were several key reviews regarding NIRS (Quaresima et al., 2003; Wolf et al., 2007). Journal articles and abstracts published from 1996 through September 2009 were considered for review in this analysis. Procedures for selecting and evaluating effects from the articles were consistent with the Quality of Reporting of Meta-analyses (QUOROM) statement where applicable (Moher et al., 1999). Fig. 1 depicts the flow of article selection and effect size retrieval.

Criteria for inclusion were the following: (1) Studies used a continuous wave, single-distance (relative change in light intensity is measured at a fixed source-detector distance) or multiple-distance (spatially resolved between two or more source-detector distances) NIRS oximeter to measure hemodynamic changes. (2) Exercise occurred in neutral ambient conditions. (3) The physical activity stimulus had to be of sufficient intensity to increase cardiac output and blood pressure. Studies using finger-tapping, hand movement, and foot movement provide valuable insight into brain activity during physical movement, but we were more interested in evaluating the effect of an exercise stimulus that elicits increases in cardiac output and blood pressure to levels associated with health outcomes or that limits human performance.

Studies were excluded if they: only sampled patients with brain injury (Fujiwara et al., 2004) or chronic fatigue syndrome (Neary et al., 2008); did not permit calculation of a proper effect size (Bhambhani et al., 2007; Heine et al., 2009; Gonzalez-Alonso et al., 2004; Miyai et al., 2001; Nielsen et al., 2001b; Nielsen et al., 2005); altered the exercise environment (e.g., temperature, barometric pressure, or oxygen); or used exercise that would not be sufficient to significantly increase both cardiac output and blood pressure (Colier et al., 1999; Hirth et al., 1996; Kleinschmidt et al., 1996; Obrig et al., 1997, 1996; Rupp and Perrey, 2009; Watanabe et al., 1996; Wriessnegger et al., 2008). Forty-four articles were located, and 25 studies met our inclusion criteria. Because the cerebral hemodynamic responses associated with exercise are dependent on cardiopulmonary factors

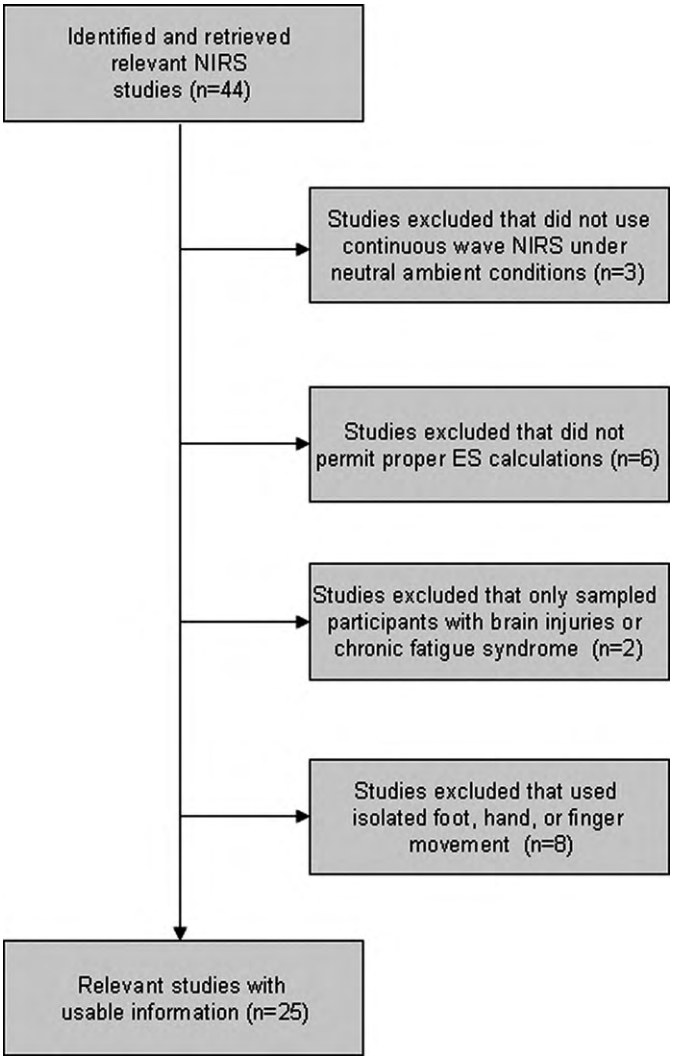

Fig. 1. Flow diagram illustrating article selection and effect size retrieval.

Table 1
Definitions for levels of effect modifiers.

Effect modifier	Levels
Age	<25: the mean age of the participants was less than 25 years 25–54: the mean age of the participants was between 25 and 54 years >54: the mean age of the participants was greater than 54 years
Exercise intensity	Low: <30% VO_2peak Moderate: ≥30% VO_2peak to <60% VO_2peak Hard: ≥60% VO_2peak to <VO_2peak Very hard: ≥VO_2peak
Health	Healthy participants: sample was reported as generally healthy Medical patients: cardiomyopathy, valvular heart disease (e.g., aortic, mitral, or tricuspid regurgitation and stenoregurgitation), coronary heart disease, and lung disease
Optode distance	≤4 cm: less than 4 cm between optodes >4 cm: greater than 4 cm between optodes
Training status	*Untrained*: authors described sample as having average aerobic fitness Average VO_2peak ($M \pm SD$) = 40.3 ± 10.4 *Trained*: authors described sample as having above-average aerobic fitness (i.e., elite cyclists, oarsmen, soldiers and triathletes) Average VO_2peak ($M \pm SD$) = 62.7 ± 7.9

(e.g., cardiac output, blood pressure, and lung functions), which are impaired in many clinical populations, analyses were conducted separately on healthy people and patients diagnosed with idiopathic dilated cardiomyopathy (Koike et al., 2004a, 2006, 2007), coronary artery disease (Nagayama et al., 2007), valvular disease (Koike et al., 2004b), or lung disease (Jensen et al., 2002).

2.2. Statistical analysis

2.2.1. Effect size calculation

Effect sizes ± 95% confidence interval were calculated as Cohen's *dz* (mean change score divided by the standard deviation of change) (Cohen, 1988), weighted by the size of the study (i.e., degrees of freedom for the effect), and then aggregated using a random effects model (Hedges and Olkin, 1985; Lipsey and Wilson, 2001). Positive effects indicate an increase in the dependent variable while negative effects indicate a decrease. Two-hundred-and-one effects were derived from 513 participants. We included 14 effects from two studies that were computed using pre-test standard deviations, so a method effect was added as a potential moderator in analyses of aggregated effects (Lipsey and Wilson, 2001). Separate effects were calculated for each dependent variable, different intensities of exercise, and for healthy participants and people with medical conditions. Dependent variables were O_2Hb, dHb, total hemoglobin (tHb; O_2Hb + dHb) and other measures of oxygenation including hemoglobin difference (O_2Hbdiff: O_2Hb − dHb) and oxygen saturation (O_2Hb/tHb) indicated by cerebral oxygen saturation (SCO_2) or tissue oxygenation index (TOI). Inter-rater agreement of effects between 2 judges was estimated by intra-class correlation (ICC-1) model one. Initial agreement was 0.90. After correction for calculation errors and resolution of discrepancies, rater agreement was 1.00.

A random effects fail-safe *k* was calculated to determine the number of effects, within a population, that would be required to reduce the significance of the overall mean effect to $p > 0.05$ (Rosenberg, 2005). Critical sample sizes for detecting the observed effects in future studies were estimated (assuming a statistical power = 0.80 and $\alpha = 0.05$) for a difference between two dependent means (i.e., matched pairs) using G*Power version 3.01 (Faul et al., 2007).

2.2.2. Variation of effects

A random effects analysis of variance using the *Q* statistic was used to detect heterogeneity of the overall effect size (Hedges and Olkin, 1985). Because overall

Table 2
Cerebral O_2Hb, O_2Hbdiff, SCO_2, dHb, and tHb effect sizes (95% CI), *p* values, sampling error, critical sample sizes, and regression contrast weights for levels of effect modifiers in healthy participants only.

Effect modifier	Contrast weights	Effects (*k*)	*dz*	95% CI	*p*-Value	Critical sample size (*N*)
O_2Hb, O_2Hbdiff, SCO_2						1-tail, 2-tail
Intensity						
Low	−(1/2)	16	0.35	−0.01 to 0.71	.058	52, 67
Moderate	1/2	21	1.34	0.89–1.80	<.001	5, 7
Hard	1/2	18	1.52	1.02–2.01	<.001	5, 6
Very hard	−(1/2)	18	0.33	−0.19 to 0.85	.217	59, 75
Training status						
Untrained	−1	43	1.04	0.66–1.42	<.001	8, 10
Trained	1	29	0.74	0.46–1.02	<.001	13, 17
Age (years)						
<25	1/2	19	1.19	0.70–1.68	<.001	6, 8
25–54	1/2	50	0.81	0.49–1.13	<.001	11, 15
>54	−1	5	1.09	0.71–1.46	<.001	7, 9
Optode distance						
<4 cm	−1	21	0.77	0.42–1.12	<.001	12, 16
>4 cm	1	51	0.99	0.66–1.31	<.001	8, 11
dHb						
Intensity						
Low	−(1/2)	10	0.26	0.01–0.51	.045	93, 119
Moderate	−(1/2)	10	0.56	0.08–1.04	.021	22, 28
Hard	1/2	10	1.25	0.55–1.96	<.001	6, 8
Very hard	1/2	13	1.37	0.66–2.08	<.001	5, 7
Training status						
Untrained	−1	23	0.72	0.32–1.12	<.001	14, 18
Trained	1	20	1.05	0.56–1.54	<.001	8, 10
Age (years)						
<25	−1	13	0.57	0.11–1.03	.016	21, 27
25–54	1	29	1.05	0.63–1.46	<.001	8, 10
>54	–	–	–	–	–	–
Optode distance						
<4 cm	−1	9	0.88	0.12–1.64	.023	10, 13
>4 cm	1	34	0.87	0.52–1.22	<.001	10, 13
tHb						
Intensity						
Low	−1	12	0.67	−0.33 to 1.68	.190	16, 20
Moderate	1/3	11	1.20	0.57–1.83	<.001	6, 8
Hard	1/3	12	1.48	1.08–1.88	<.001	5, 6
Very hard	1/3	10	1.57	0.83–2.31	<.001	5, 6
Training status						
Untrained	−1	24	1.17	0.59–1.75	<.001	7, 8
Trained	1	21	1.26	0.80–1.71	<.001	6, 8
Age (years)						
<25	1	11	1.78	0.80–2.76	.001	4, 5
25–54	−1	34	1.02	0.77–1.33	<.001	8, 10
>54	–	–	–	–	–	–
Optode distance						
<4 cm	−1	11	0.94	−0.06 to 1.94	.065	9, 11
>4 cm	1	34	1.30	0.94–1.67	<.001	6, 7

effects were heterogeneous (Q reached a significance of $p \leq 0.05$ and sampling error explained less than 75% of the observed variance), a moderator analysis was performed to explain between-study variation in healthy samples. Types and levels of potential effect moderators were defined based on features of the exercise stimulus, characteristics of the participants, and differences in NIRS methodology. A list of the moderators and their definitions is presented in Table 1. Based on theoretical and practical interests, focused contrast weights (Rosenthal and DiMatteo, 2001) were assigned to levels of each moderator and tested by z-scores (Table 2). Sensitivity analyses were conducted by re-estimating moderator effects after any outlying effects were removed (Grubbs and Beck, 1972). Partial pressure of end-tidal carbon dioxide ($PETCO_2$) was also determined for studies that provided those values or measured partial pressure of arterial carbon dioxide ($PaCO_2$). One study (Seifert et al., 2009) included a measure of $PaCO_2$ in units of kPa. These values were converted to units of mmHg for consistency. All other studies presented $PaCO_2$ or $PETCO_2$ values in interchangeable units of Torr or mm Hg. Forest plots were produced using MIX version 1.7 (Bax et al., 2008, 2006).

2.2.3. Meta-regression

The contrast-weighted variables were then entered into a mixed model weighted multiple linear regression with maximum likelihood estimation (ML) (SPSS Windows version 16; SPSS Inc., Chicago, IL) to determine independent main effects and interactions (Lipsey and Wilson, 2001). Variance explained (Q_R) and not explained (Q_E) was tested. The number of effects per study was added to the model to adjust for potential bias resulting from non-independence of multiple effects derived from a single study (Gleser and Olkin, 1994); there was no bias, so the number of effects per study was excluded from further models. VO_2peak (i.e., peak oxygen uptake) was included in all regression models to adjust for some variation of $\%VO_2$peak within each level of the exercise intensity variable. An insufficient number of effects was available from studies of patients, limiting regression analysis to healthy samples.

3. Results

3.1. Healthy people

Participants (N = 291) from 21 studies had a mean age (years) of 30.9 ± 11.8 SD and mean VO_2peak (ml min^{-1} kg^{-1}) of 48.5 ± 14.5 SD. Twenty percent were women, but only 1 study provided results for women (Neary et al., 2008). Contrast weights, effect sizes (95% CI), and their associated p-values for each level of the moderator variables are presented in Table 2 for cerebral oxygenation, dHb, and tHb. There were not enough results reported to yield good estimates of effects for dHb and tHb in some levels of the moderators. Estimates of critical sample sizes for each effect are also provided.

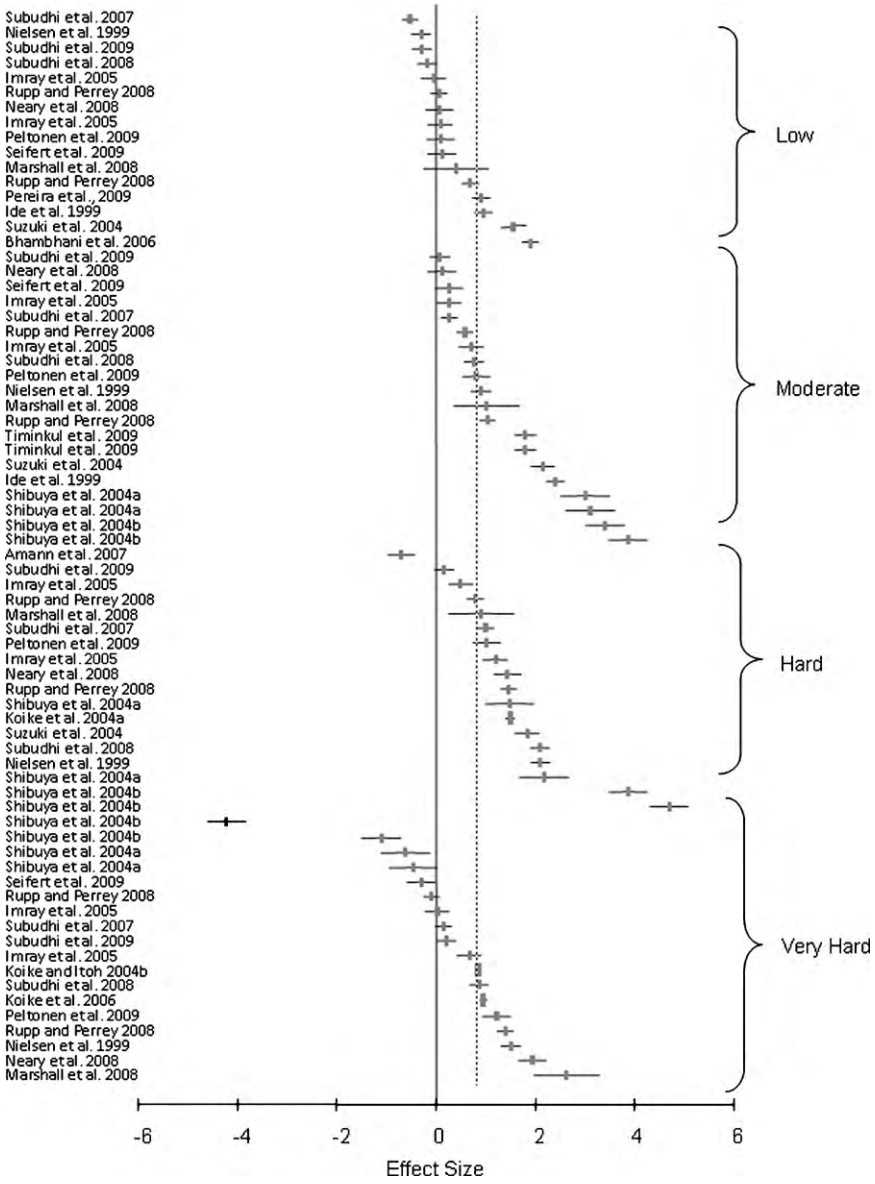

Fig. 2. Forest plots showing the distribution of effect sizes for O_2Hb, $O_2Hbdiff$, and SCO_2 according to exercise intensity. Values are presented as mean dz ± 95% CI. Overall mean is represented by a vertical dotted Amann et al., 2007; Imray et al., 2005; Saitou et al., 2000; Shibuya et al., 2004a, 2004b; line.

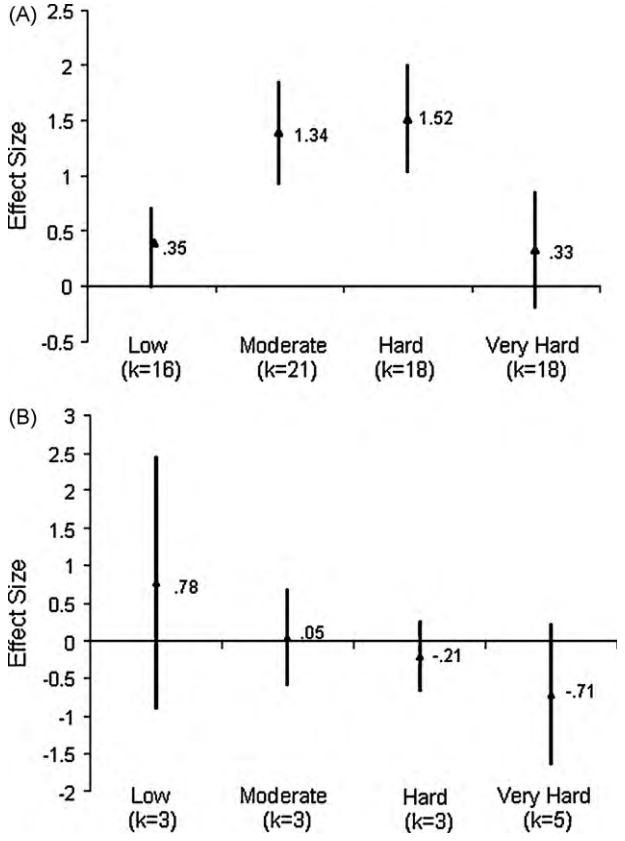

Fig. 3. Effect of exercise on cerebral (A) O_2Hb, $O_2Hbdiff$, SCO_2 (B) TOI across low, moderate, hard, and very hard intensities in healthy people. Number of effects = *k*. Values are presented as mean *dz* ± 95% CI.

3.1.1. Cerebral O_2Hb, $O_2Hbdiff$, SCO_2

Exercise resulted in a large, heterogeneous increase in measures of cerebral oxygenation (O_2Hb, $O_2Hbdiff$, SCO_2), $dz = 0.92$ (95% CI, 0.67–1.17), $p < .001$, $k = 72$, $Q = 735.2$, d.f. 71, $p < .001$, sampling error 37.9% (Fig. 2). Fail-safe *k* was 9228. Effects for O_2Hb, $dz = 0.93$ (95% CI, 0.67–1.19), were not different from effects for $O_2Hbdiff$, $dz = 1.15$ (95% CI, 0.08–2.21), and SCO_2, $dz = 0.64$ (95% CI, 0.18–1.11). Effects for TOI, $dz = -0.11$ (95% CI, −0.59 to 0.37), $k = 14$, were lower than the other measures at moderate and hard intensities (see Fig. 3A), so they were excluded from the regression models. The regression model including all moderators (Table 1) ($Q_R(5) = 25.93$, $p < 0.001$, $R^2 = 0.27$; Q_E (61) = 69.35, $p = .22$) indicated that intensity of exercise was the only variable that independently modified effect size ($\beta = 0.48$, $z = 4.63$, $p < .001$), and this influence was unchanged after further accounting for VO_2peak. Effects followed a quadratic trend across intensity with larger effects at moderate and hard intensity levels compared to low and very hard intensities (Fig. 3A and B). Effects of exercise intensity on $PETCO_2$ followed a quadratic trend similar to cerebral oxygenation, except at low intensities (Fig. 4).

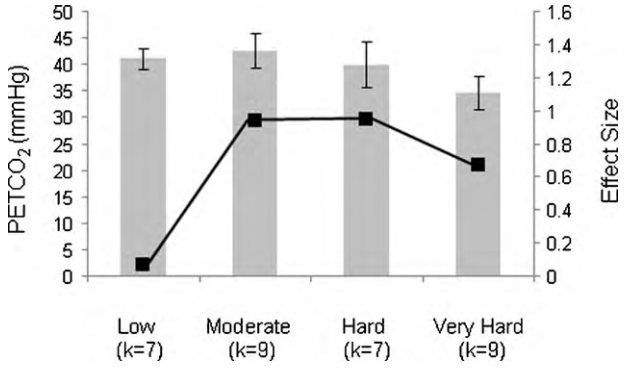

Fig. 4. Effect of exercise on cerebral O_2Hb, $O_2Hbdiff$, and SCO_2 in studies also reporting $PETCO_2$ across low, moderate, hard, and very hard intensities in healthy people.

A second regression model including interactions ($Q_R(6) = 32.56$, $p < 0.001$, $R^2 = 0.32$; $Q_E(60) = 68.91$, $p = .20$) indicated an intensity × training status effect of exercise on cerebral oxygen ($\beta = -0.59$, $z = -2.23$, $p = .03$). Follow-up contrasts revealed that, compared to untrained participants, those who were aerobically trained had significantly lower (mean ± 95% CI) cerebral oxygen levels during low (0.01 ± −0.33, 0.34 vs. 0.60 ± 0.07, 1.12), moderate (0.73 ± 0.49, 0.97 vs. 1.74 ± 1.05, 2.44), and hard (1.11 ± 0.52, 1.70 vs. 1.86 ± 1.08, 2.64) intensity exercise, and significantly higher levels during very hard intensity exercise (1.02 ± 0.43, 1.68 vs. −0.15 ± −0.92, 0.61). See Fig. 5A.

3.1.2. Cerebral dHB

Exercise resulted in a moderately large, heterogeneous increase in dHb, $dz = 0.87$ (95% CI, 0.56–1.19), $p < .001$, $k = 43$, $Q = 404.2$, d.f. 42, $p < .001$, sampling error 15.6% (Fig. 6). Fail-safe *k* was 3255. An outlying effect from (Rupp and Perrey, 2008) was excluded after a sensitivity analysis. The regression model including all moderators ($Q_R(5) = 17.59$, $p = 0.004$, $R^2 = .29$; $Q_E(37) = 43.75$, $p = .21$) indicated that intensity was the only independent moderator of dHb during exercise ($\beta = 0.45$, $z = 3.48$, $p = .001$).

A second model including interactions ($Q_R(6) = 26.30$, $p = 0.002$, $R^2 = 0.38$; $Q_E(36) = 43.60$, $p = .18$) revealed an intensity × training status effect ($\beta = 0.30$, $z = 2.48$, $p = .01$). Follow-up contrasts indicated that compared to untrained participants, aerobically trained participants had significantly higher (mean ± 95% CI) dHb levels during hard (1.64 ± 0.74, 2.55 vs. 0.66 ± −0.49, 1.81) and very hard intensities (2.00 ± 1.32, 2.68 vs. 0.99 ± −0.05, 1.93) (Fig. 5B). VO_2peak was positively related to increases in dHb at hard and very hard intensities but not at low and moderate intensities (Fig. 7).

3.1.3. Cerebral blood volume

Exercise resulted in a large, heterogeneous increase in tHb, $dz = 1.21$ (95% CI, 0.84–1.59), $p < .001$, $k = 45$, $Q = 599.3$, d.f. 44, $p < .001$, sampling error 2.8% (Fig. 8). Fail-safe *k* was 7348. The regression model including all moderators was significant ($Q_R(5) = 11.16$, $p = 0.05$, $R^2 = 0.20$; $Q_E(37) = 44.59$, $p = .18$) indicating that intensity ($\beta = 0.29$, $z = 2.16$, $p = 0.03$) and age ($\beta = -0.31$, $z = -2.21$, $p = .03$) independently moderated tHb during exercise.

A second model of interactions ($Q_R(6) = 16.67$, $p = 0.01$, $R^2 = 0.27$; $Q_E(36) = 44.93$, $p = .15$) indicated an intensity × training training status ($\beta = 0.27$, $z = 2.06$, $p = .04$) effect. Contrasts revealed that compared to untrained participants, those who were aerobically trained had significantly lower levels of tHb at low intensity (−0.07 ± −0.37, 0.22 vs. 1.15 ± −0.30, 2.60) but higher tHb at hard (1.81 ± 1.46 vs. 1.19 ± 0.56, 1.82) and very hard (2.49 ± 1.44, 3.55 vs. 0.68 ± −0.06, 1.36) intensities (Fig. 5C).

3.2. Patients

Patients ($N = 222$) from 6 studies had a mean age (years) of 60 ± 3.0 SD and mean VO_2peak (ml min^{-1} kg^{-1}) of 18.3 ± 2.7 SD. Twenty-five percent were women, but no study provided results only for women. The heterogeneous, overall mean effect of exercise in patients was $dz = -0.26$ (95% CI, −0.57 to −0.04), $p = .09$, $k = 22$, sampling error 29.70%. Exercise resulted in moderate reductions or no change in cerebral oxygenation $dz = -0.36$ (95% CI, −0.77 to 0.04), $p = .08$, $k = 12$, sampling error 29.70% and dHb $dz = -0.32$ (95% CI, −1.01 to 0.36), $p = 0.36$, $k = 7$, sampling error 3.04%, and no change or

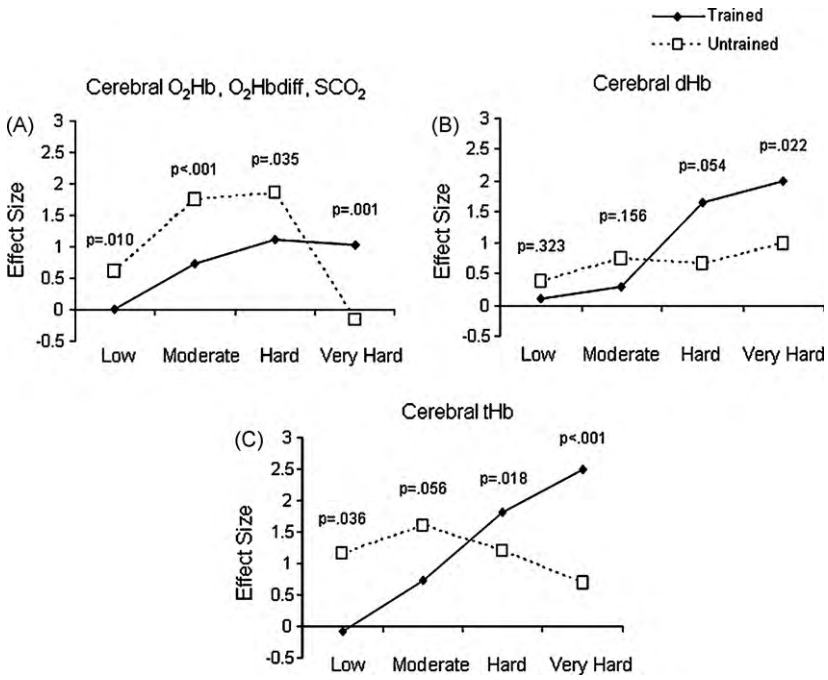

Fig. 5. Effects of exercise on (A) cerebral O_2Hb, $O_2Hbdiff$, SCO_2, (B) dHb, and (C) blood volume (tHb) at low, moderate, hard, and very hard intensities in aerobically trained and untrained individuals.

a small increase in tHb $dz = 0.30$ (95% CI, −0.15 to 0.74), $p = .19$, $k = 3$, sampling error 53.76%. Effects for oxygenation were similar for moderate intensity exercise (-0.55 ± -1.92, 0.82, $k = 2$) and very hard intensities (-0.22 ± -0.70, 0.27, $k = 8$). Likewise, effects of moderate (-0.94 ± -2.62, 0.74, $k = 2$) and very hard (0.34 ± -0.24, 0.92, $k = 3$) intensities on dHb were not statistically different. The small number of effects for tHb did not allow comparison across intensities. Mean effects ± (95% CI) according to medical condition were: idiopathic dilated cardiomyopathy $-0.92 \pm (-1.60$ to $-0.24)$, $k = 9$), other heart and valvular diseases $0.03 \pm (-0.33$ to $0.39)$, $k = 4$), and lung disease $0.23 \pm (-0.07$ to $0.53)$, $k = 9$).

4. Discussion

The results of this systematic, quantitative review support and extend several conclusions of prominent narrative reviews that evaluated the influence of exercise on brain blood flow and metabolism using NIRS and other methods (Dalsgaard, 2006; Ide and Secher, 2000; Nybo and Secher, 2004; Ogoh and Ainslie, 2009b; Secher et al., 2008). Ide and Secher concluded that HbO_2 and tHb increase during dynamic sub-maximal exercise, but at levels of intense, exhaustive exercise dHb increases while cerebral oxygen saturation decreases. The results reported here are consistent with the conclusions of that review, showing that during sub-maximal exercise, oxygen and blood volume to the prefrontal cortex increase, but dHb levels rise higher than oxygen at maximal intensities, implying a reduced supply of oxygen relative to demand. This latter effect might be explained by an augmented shunting of blood flow to working muscle (Rowell, 1974), by a protective plateau or decline in cardiac output (Gonzalez-Alonso and Calbet, 2003; Noakes, 1998), or hypocapnia leading to cerebral vasoconstriction during maximal intensity exercise.

The heterogeneity of effects reported here is explainable in part by exercise intensity, training status, age, and health status. Different spectroscopy methods did not influence study outcomes, but most studies used similar methods. In the following discussion, influences by these moderators of cortical metabolism or its measurement during exercise will be addressed. In addition, some testable hypotheses and methodology advances will be suggested for future research that can elaborate the understanding of putative influences on cerebral hemodynamics assessed by NIRS during incremental exercise.

4.1. Exercise intensity

As depicted in Fig. 3A, the rise in cerebral oxygen level with increasing exercise intensity followed a quadratic trend. Oxygenation initially increased between low and moderate intensities, remained stable from moderate-to-hard intensities, and then declined at very hard or maximal, exhaustive intensities. Cerebral oxygen levels during very hard exercise dropped to values similar to those observed during low intensity exercise. These effects are tightly linked to peripheral hemodynamic changes from low to moderate intensities (e.g., increased cardiac output, via CNS integration of arterial and cardiopulmonary baroreflexes and neural input from metabo- and mechano-receptors from skeletal muscle) and to changes in arterial blood gases from moderate-to-hard or maximal intensities (e.g., decreasing $PaCO_2$), which illustrates the need to measure the exercise stimulus precisely. The results of our analysis are inconsistent with the 'transient hypofrontality' hypothesis, which speculates that during sub-maximal exercise, neural activity is down-regulated in brain areas not directly involved in motor control, such as the prefrontal cortex (Dietrich, 2003). According to Dietrich, "studies on cerebral blood flow and metabolism have provided the strongest support for the hypothesis that exercise decreases neural activity in the prefrontal cortex" (Dietrich, 2006, p. 81). The pattern of cerebral oxygenation, deoxygenation, and blood volume presented here suggests the opposite. Only during highly intense, exhaustive exercise were cerebral oxygen values lowered. In contrast, moderate-to-hard sub-maximal exercise was accompanied by increases in cerebral oxygen and blood volume.

It has been suggested that reductions in cerebral oxygenation during exhaustive intensities are caused by decreased cerebral blood flow coupled with increased cerebral oxygen uptake

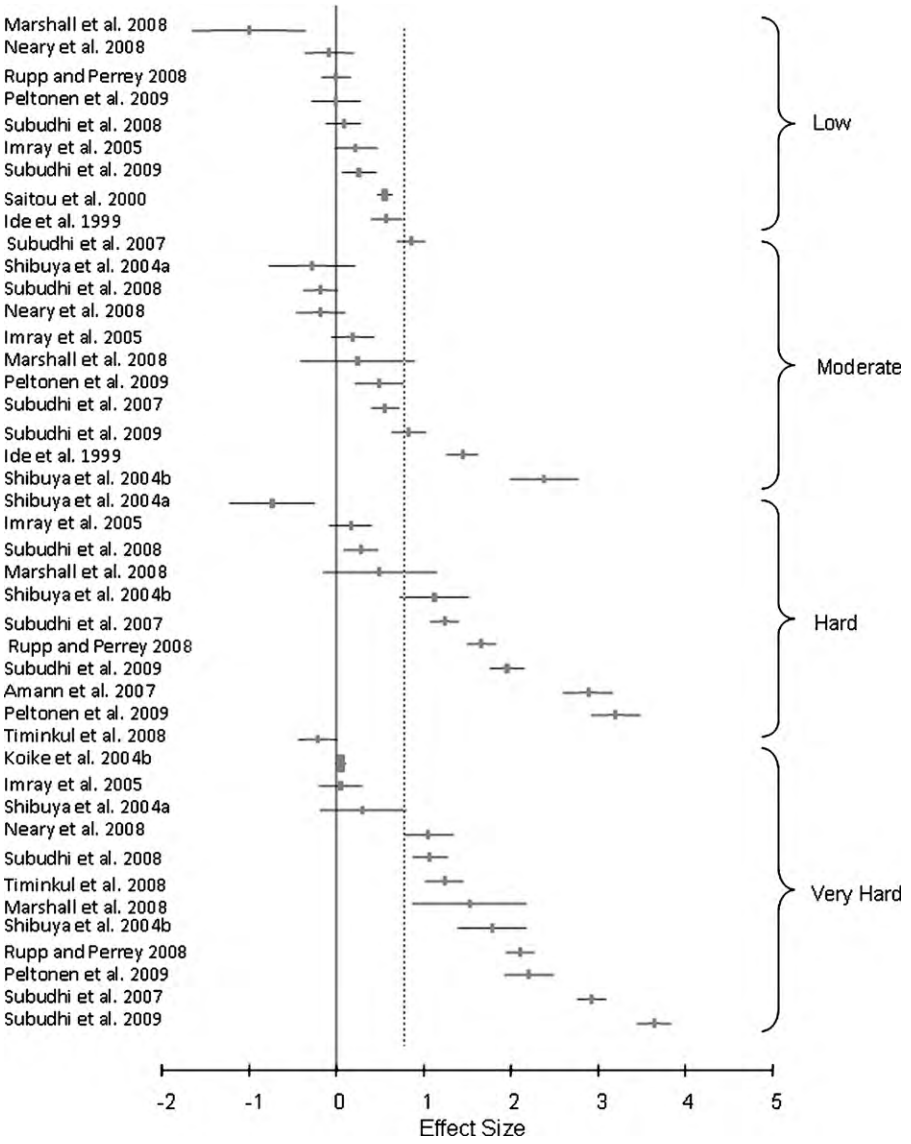

Fig. 6. Forest plots showing the distribution of effect sizes for dHb according to exercise intensity. Values are presented as mean $dz \pm 95\%$ CI. Overall mean is represented by a vertical dotted line.

(Gonzalez-Alonso et al., 2004). It has also been proposed that this change in flow and metabolism at high intensities is sensed or controlled by a 'central governor' so that during times when oxygen availability is reduced, peak exercise performance is reduced to prevent the development of ischemia in vital organs including the brain and heart (Noakes, 1998; Noakes et al., 2005).

The predominant models set forth to explain central fatigue or the decision to stop during maximal or prolonged sub-maximal exertion include cardiovascular/neural recruitment and biochemical signaling. Central drivers from the motor cortex, sub-cortical locomotory circuits, or motor neurons, can override strong somatic, visceral and 'homeostatic' circuits that can stop ongoing exercise when they are activated. Conversely, putative brain mechanisms of impaired voluntary activation of motor neurons during prolonged, strenuous exercise include an effective decrease in supraspinal motor drive to motor neurons (Gandevia, 2001). Reduced motor drive during maximal or prolonged sub-maximal exercise may be associated with increased brain serotonin activity, elevated ammonia levels, brain glycogen depletion, a reduced metabolic ratio (i.e., the brain's uptake of oxygen relative to the oxidation of carbohydrate), decreased striatal dopamine, and inhibitory feed-back from the exercising muscles (Amann et al., 2008b; Amann and Secher, 2010; Dalsgaard and Secher, 2007; Nybo and Secher, 2004). The work of breathing and high intra-thoracic pressure are significant influences on cardiac output, perceived exertion, and peripheral and central fatigue in heart and lung patients (Dempsey et al., 2008).

The 'central governor' hypothesis proposes that the brain anticipates homeostatic threats and subsequently reduces motor output to decrease muscle unit recruitment, thereby constraining cardiac output in order to maintain cardiac and cerebral function (Noakes et al., 2001; Noakes and Marino, 2009; St Clair Gibson et al., 2001). It has also been suggested that the reduction in efferent motor command can be explained by metabolic changes in higher cortical brain structures (Noakes and St Clair Gibson, 2004; St Clair Gibson and Noakes, 2004; St Clair Gibson et al., 2001). In this way, an increase in dHb and a decrease in cerebral oxygenation represent potential metabolic indicators, signaling either directly or indirectly to sub-cortical and cortical motor areas of the brain to reduce muscle unit recruitment and thus protect the brain and peripheral organs. This argument is consistent with the presence of neural projections from the prefrontal cortex to pre-motor areas

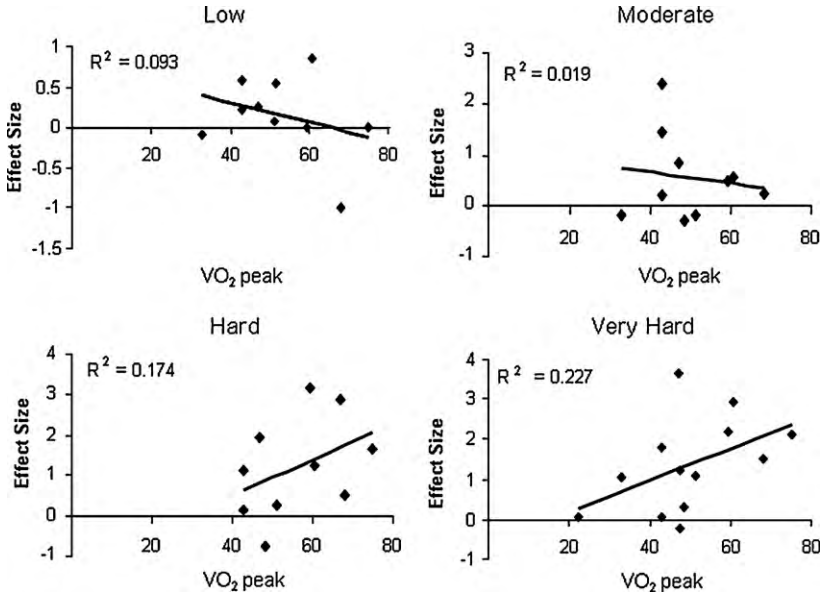

Fig. 7. Scattergrams of VO_2peak and dHb effects at low, moderate, hard, and very hard intensities.

and with the association of decreased prefrontal oxygenation with decreased force production by muscle contraction (Rasmussen et al., 2007). Key postulates of the 'central governor' hypothesis are that both motor drive from the brain and cardiac work are at their true maximums at the point of maximal performance (e.g., VO_2max) (Noakes and Marino, 2009; each has been disputed (Ekblom, 2009; Shephard et al., 2009). Cardiac output or local muscle fatigue can limit maximal exercise performance, depending upon the mode of exercise (e.g., *in situ* muscle activation, single limb isometric maneuvers, leg cranking, combined arm and leg cranking, or treadmill running) or ambient conditions (e.g., extreme heat or high altitude). However, even in normal, non-hostile ambient conditions healthy people often fatigue or choose to terminate exercise before they reach a plateau in oxygen uptake (Jones and Killian, 2000; Kayser, 2003). Identification of the precise roles of the brain and spinal cord in regulating perceived exertion, motivation, and central fatigue (i.e., a progressive decline in the central neural drive to motor neurons) (Gandevia, 2001) to influence cardiac and skeletal muscle by central command or in response to sensory and metabolic signals produced during exhaustive, incremental or prolonged exertion remains elusive. Advances in understanding these roles will require use of technologies that better measure (e.g., NIRS) and manipulate specific central and peripheral determinants of performance within integrative physiological models (Amann et al., 2008a,b; Hargreaves, 2008).

The summary results from our analysis suggest a decline in oxygen saturation and blood volume at the very highest exercise intensities in people who are aerobically untrained, which is consistent with the central governor hypothesis (Noakes et al., 2005). However, reduced blood flow and oxygenation to the frontal cortex at hard and very hard exercise intensities occur concurrently with decreased $PaCO_2$ after the respiratory compensation threshold (e.g., Bhambhani et al., 2007). Thus, although reduced blood volume or $PaCO_2$ might be sensed by a central governor, they alternatively might be linked physiologically without invoking anticipatory regulation by a brain governor.

The hypocapnia that accompanies hyperventilation during exhaustive exercise leads to cerebral vasoconstriction and reduced cerebral blood flow (Bhambhani et al., 2007; Nielsen et al., 1999). Early studies indicated that the autoregulation of cerebral blood flow is largely determined by $PaCO_2$ and mean arterial pressure between 60 and 150 mm Hg. Increasing levels of $PaCO_2$ are accompanied by vasodilation and increased blood flow, while lowered $PaCO_2$ levels can lead to cerebral hypoperfusion (Paulson et al., 1990). Less than half the studies we reviewed here reported $PaCO_2$ or its indirect index $PETCO_2$, precluding a strong test of its relation with cerebral hemodynamics in our analysis. Nonetheless, in those studies, effects of exercise intensity on $PETCO_2$ followed a quadratic trend similar to cerebral oxygenation, consistent with prior evidence that cerebral oxygen levels follow $PaCO_2$ during incremental exercise (Ide and Secher, 2000). The similar trends of cerebral oxygen and $PETCO_2$ at moderate-to-very hard intensities observed here were confirmed in several studies that precisely controlled increments in exercise intensity (Subudhi et al., 2007; Rupp and Perrey, 2008). In those studies, $PETCO_2$ levels increased during sub-maximal intensities (25 to >50% VO_2peak) and decreased at maximal exertion. Bhambhani et al. (2007) and Rupp and Perrey (2008) reported that $PETCO_2$ levels during incremental exercise increase until the respiratory compensation threshold (RCT) is reached and then decrease until maximal intensity exercise. Lowered blood pH, which occurs at intensities that correspond to the RCT, stimulates the hyper-ventilatory response necessary to reduce $PaCO_2$ and help balance blood pH. In those studies, cerebral oxygenation and blood flow levels began to decline with decreases in $PETCO_2$ immediately after RCT was reached, which is commonly 75–90% of VO_2peak during leg cycling, depending on training status (Bhambhani et al., 2007; Bussotti et al., 2008; Dekerle et al., 2003).

Recent studies using transcranial Doppler ultrasound to estimate global cerebral blood flow by measuring middle cerebral artery velocity suggest that blood flow begins to decrease toward baseline after peaking around 60% of VO2peak (Ogoh and Ainslie, 2009a, 2009b). Most of the studies we retrieved for this review provided the information needed to express incremental exercise intensity relative to VO_2peak but not according to more precise indexes of metabolic strain (e.g., lactate or ventilatory thresholds, respiratory compensation threshold, or critical power) that might better account for associations between maximal performance and hemodynamic responses measured systemically and in the brain that are influenced by arterial gases and metabolic by-products

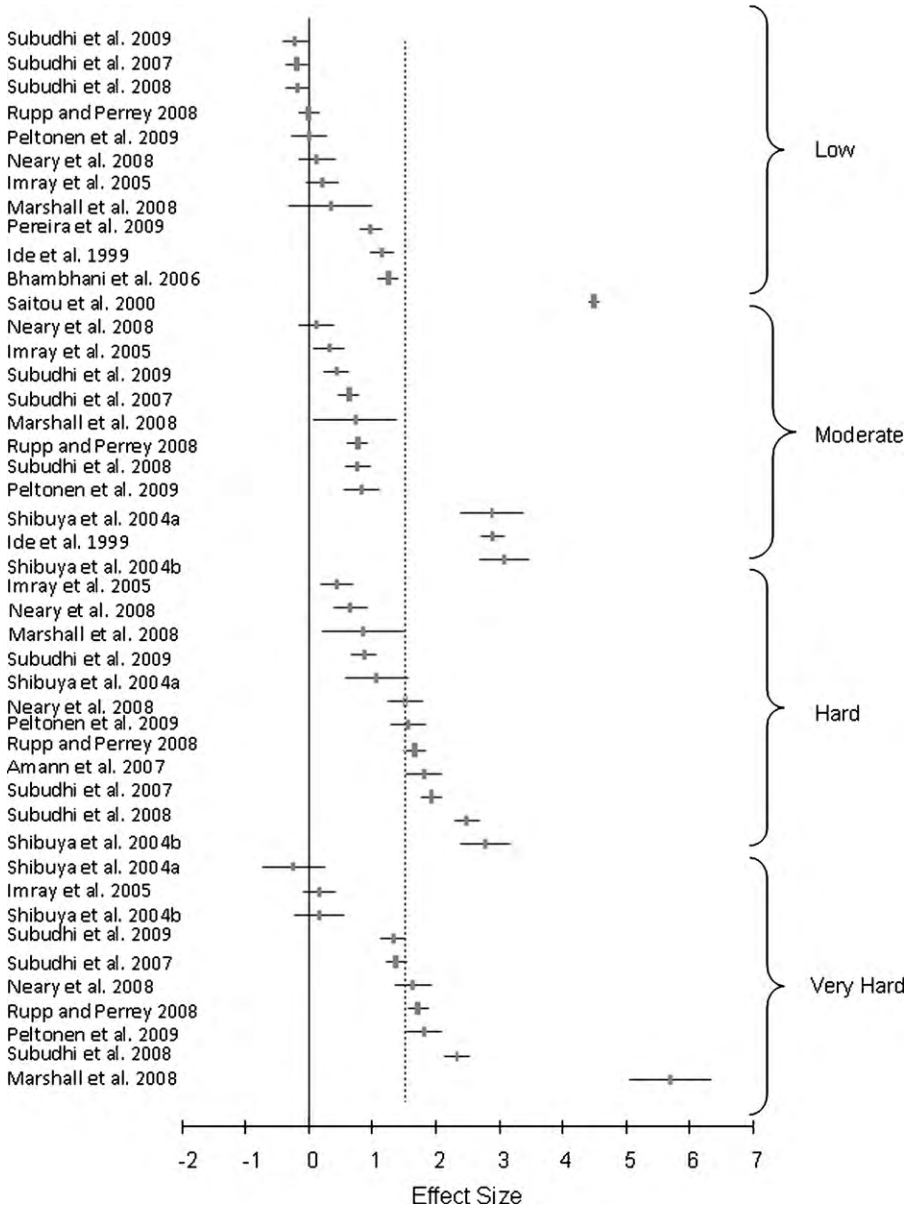

Fig. 8. Forest plots showing the distribution of effect sizes for tHb according to exercise intensity. Values are presented as mean *dz* ± 95% CI. Overall mean is represented by a vertical dotted Amann et al., 2007; Imray et al., 2005; Saitou et al., 2000; Shibuya et al., 2004a, 2004b; line.

associated with muscle metabolism. The levels of moderate (≥30% VO_2peak to <60% VO_2peak) and hard (≥60% VO_2peak to <VO_2peak) intensities used here are consistent with consensus definitions of hard or vigorous physical activity (Physical Activity Guidelines Advisory Committee, 2008) and would distinguish intensities below and above ventilatory threshold for most participants in the studies we reviewed, but they do not precisely identify the respiratory compensation threshold or account for the effect of aerobic training.

In the studies of healthy people reviewed here, increases in cerebral oxygen were accompanied by increases in dHb and tHb at hard intensities. However, as the intensity increased to maximal, exhaustive levels, dHb values did not decline like cerebral oxygen levels. Instead, dHb remained elevated during hard and very hard intensities, particularly in people who were aerobically trained. Levels of tHb followed a similar trend as cerebral oxygenation, peaking at hard intensities and then decreasing at the highest intensity among untrained, but not trained, participants. This implies that blood volume to the brain is not sacrificed, but it does start to fall toward baseline levels, during exhaustive exercise in untrained people without impaired left ventricular function. It appears that there is a shift in metabolic balance at exhaustive intensities, with the consumption of oxygen surpassing its availability. Thus, blood volume in the frontal cortex seems to decline at maximal exertion, consistent with previous research (Gonzalez-Alonso et al., 2004), but only in people who are not aerobically trained. Because NIRS predominantly measures venous hemoglobin, the different responses of dHb observed here for trained and untrained participants at very hard intensities is difficult to interpret as differences in cerebral blood flow. A recent study of incremental leg cycling to exhaustion (Timinkul et al., 2008) reported a similar quadratic response during incremental leg cycling in levels of O_2Hb that began before lactate threshold (at about 40–45% VO_2peak), peaked, and then declined with a concurrent reduction in the TOI and an increase in dHb, each suggesting cerebral oxygen desaturation prior to voluntary exhaustion.

In brain, as well as other tissues, there appears to be a proportional increase in blood flow with increasing metabolic intensity, but the mechanisms for increased cerebral blood flow

during incremental exercise are as yet unknown. As observed in skeletal muscle, prefrontal cerebral blood flow during incremental, sub-maximal dynamic exercise (e.g., Rupp and Perrey, 2008), but not sustained, static exercise (Pereira et al., 2009), appears to be coupled with oxygen demand. However, our meta-analytic results suggest that a different mechanism influences blood flow and oxygen delivery to the frontal cortex. The hyperoxia that accompanies incremental, sub-maximal exercise suggests that the control of hyperemic blood flow during exercise in aerobically trained people is not directly linked to blood oxygen levels. There are many vasodilating mechanisms (e.g., potassium, adenosine, ATP, H+, endothelial and neuronal nitric oxide) in addition to low O_2 that can explain cerebral hyperemia. Rather than being regulated to deliver oxygen, increased blood flow during incremental sub-maximal exercise could be regulated to maintain fuel availability (e.g., glucose delivery). At the highest exercise intensities, limitations in cardiac output or decreasing $PaCO_2$ could limit the delivery of oxygen to the brain, or increased neural activity at the highest intensities could exceed the delivery of oxygen to the brain such that oxygen levels in cerebral blood fall. This would suggest that at the highest exercise intensities there is inadequate delivery of oxygen, which could lead to compromised brain function (e.g., decreased motor drive). Patients with compromised circulatory function show evidence of reduced oxygen levels at relatively low exercise intensities, suggesting impairments in brain blood supply or brain function.

4.2. Training status

Increases in cerebral oxygenation, dHb, and tHb varied widely between aerobically trained and untrained participants according to exercise intensity (Fig. 5). At low and moderate intensities, trained people had lower cortical oxygenation and lower blood volume than did untrained individuals, suggesting a lower cortical metabolic demand. In contrast, aerobically trained participants attained higher levels of cortical oxygen, dHb, and tHb than did untrained participants during maximal, exhaustive intensities. After peaking at hard intensities, oxygen values dropped at very hard intensities in untrained participants but not in trained participants. Nonetheless, dHb increased markedly in trained people, implying an increase in oxygen demand that was greater than oxygen supply. In untrained participants, the drop in oxygen levels was severe and was accompanied by a drop in blood volume. The putative decline in oxygen saturation between hard and very hard intensities in trained participants may have been underestimated, though. Two studies of trained cyclists reported TOI values at maximal intensity that were about 2 SD below baseline (Marshall et al., 2008; Peltonen et al., 2009), which contrasts with other reports on trained participants that levels of O_2Hb and tHb remained similarly elevated at maximal intensities despite hypocapnia (e.g., Subudhi et al., 2008; Rupp and Perrey, 2008; Marshall et al., 2008).

One explanation for these results might be that adaptations to exercise training down-regulate sensory signaling from muscle and limbs to the central nervous system and, thus, reduce somatosensory input to sub-cortical and cortical brain areas involved with central command, especially at sub-maximal intensities (Gandevia, 2001). The gain of motor neurons decreases during sustained activation, so an increase in motor drive is necessary to continue prolonged, constant-load exercise (Gandevia, 2001). However, it is established that muscle afferents that are sensitive to ischemia can decrease supraspinal motor drive to motor neurons (Gandevia et al., 1996). Likewise, altered input from muscle spindle, tendon organ, and groups III and IV muscle afferents from fatiguing muscle act to reduce motor neuron activation at spinal segment sites and the brain cortex (Butler et al., 2003; Gandevia, 2001; Taylor and Gandevia, 2008). Down-regulation of signaling from skeletal muscle afferents and the arterial baroreflex in highly trained people could explain reduced cerebral blood flow and oxygenation at sub-maximal intensities of exercise. Conversely, it is possible that repeated CNS exposure to high neural input from fatiguing muscle might desensitize a 'central governor', permitting the attainment of higher intensities of effort and greater homeostatic challenge to cerebral homeostasis among people who are aerobically trained. Alternatively, lowered peripheral chemosensitivity and minute ventilation, which are commonly seen in aerobically trained individuals (reviewed by Weil and Swanson, 1991), might attenuate reductions in $PaCO_2$ during hard-to-maximal exercise intensities, resulting in less vasoconstriction and higher estimates of blood volume and cerebral oxygenation as measured by NIRS.

It is likely that untrained participants were less likely to have reached a VO_2peak that approximated their aerobic capacity (i.e., VO_2max or a plateau in VO_2 with increasing intensity) than were trained participants (Noakes, 1998). The observation that trained participants attained higher VO_2peak and higher O_2Hb, dHb, and tHb at very hard intensities than did untrained participants, when coupled with the positive relation between VO_2peak and increases in dHb observed only at hard and very hard intensities, seems inconsistent with the 'central governor' hypothesis when applied to incremental, maximal exercise. However, few of the studies we reviewed included convergent indicators of near maximal effort (e.g., blood lactate, respiratory exchange ratio, or ratings of perceived exertion) by untrained people, so this explanation is hard to judge.

4.3. Age

Cerebral oxygenation during brain activation is inversely related to age (Hock et al., 1995; Mehagnoul-Schipper et al., 2002), implying either that oxygen availability is lower or blood volume to cortical areas is reduced in older people. Among the studies reviewed here, cerebral oxygen levels during exercise were not statistically different in healthy people over 55 compared to healthy people aged 25–54, and <25 years of age. However, there were only 5 effects from studies of healthy people over age 54 years of age, reducing the likelihood of detecting a significant effect of age on cerebral oxygenation. In contrast, tHb levels were lower during exercise for individuals between the ages of 25–54 compared to individuals <25 years of age. This age effect was not independent of the other effect moderators, and it is difficult to interpret because none of the studies we located provided a measure of dHb or tHb for healthy people over 54 years of age.

4.4. Health status

People with medical conditions had a reduction or no change in brain oxygenation and blood volume during moderate and very hard intensities compared to rest. Those results are consistent with their lower absolute working capacity, as evidenced by lower VO_2peak than expected for their age. Various lung diseases, which are associated with impaired oxygen transport, cause O_2Hb to decrease or remain unchanged and dHb, and tHb to increase during incremental exercise to peak intensities (Jensen et al., 2002). On the other hand, cardiovascular diseases such as cardiomyopathy decrease O_2Hb to critical levels during exercise (Koike et al., 2004a, 2006, 2007). In studies reviewed here (Koike et al., 2004a, 2006), cerebral O_2Hb was positively correlated with peak VO_2 and left ventricular ejection fraction. The reduced left ventricular ejection fraction and peak VO_2 observed in patients with cardiomyopathy are indicative of inadequate cardiac output. This would account for

reduction in cerebral O_2Hb potentially caused by lower blood volume and hypoperfusion.

Other studies have shown hemodynamic abnormalities among patients with cardiovascular disease (Itoh et al., 1989; Weber and Janicki, 1985; Weber et al., 1982). Lee et al. (1999) reported that heart failure was related to abnormal cerebral metabolism measured by proton magnetic resonance spectroscopy that was primarily the result of cerebral hypoperfusion. Because we located only a few studies that used NIRS during exercise by patients diagnosed with cardiomyopathy, it is not possible to infer that cerebral hypoperfusion is the primary cause of their abnormal hemodynamic changes during exercise. Variables such as cardiac output, blood pressure, VO_2, and the $PaCO_2$ undoubtedly play a role and should be assessed in future NIRS studies of cerebral oxygenation and metabolism during exertion by heart and lung patients.

4.5. NIRS methodology

We used O_2Hb, $O_2Hbdiff$ and SCO_2, but not TOI, as measures of cerebral blood oxygenation in our analyses. Studies that used TOI reported a decline at very hard exercise intensities, consistent with results for measures of HbO_2, $O_2Hbdiff$ and SCO_2, but TOI did not appear to change during increments from low-to-hard intensities despite apparent increases in O_2Hb that exceeded increases in dHb (Marshall et al., 2008; Neary et al., 2008; Peltonen et al., 2009; Timinkul et al., 2008). It will be important for investigators to consider or explain this seeming discrepancy when interpreting similarly discordant results for TOI in future studies. Both TOI and SCO_2 are defined as the ratio of HbO_2 to tHb and each quantifies oxygen saturation by a subtraction algorithm that helps removes extracerebral sources of light absorption. However, they are measured using different methods and provide values that only moderately agree during CO_2 challenge (Yoshitani et al., 2002). We recommend that future studies using these ratios consider the relative contributions of changes in HbO_2 and dHb to tHb during incremental exercise and how those contributions may influence the interpretation of TOI and SCO_2 as equivalent indicators of cerebral oxygen saturation.

Effects of exercise on cerebral oxygen or dHb were not modified by optode distance, which ranged from 3 to 5 cm. Depth of the NIRS signal is proportional to optode distance (approximately 60%), with larger distances providing information from deeper tissue (Choi et al., 2004). Others have reported that distances >5 cm are required to decrease sensitivity to superficial tissue and increase information obtained from the underlying cerebral tissue (Germon et al., 1999). Changes in oxygenation measures and dHb observed here were highly variable, with effects for O_2Hb and tHb tending to be larger when distances exceeded 4 cm. This is consistent with the argument that distances between 3 and 4 cm are less accurate (Germon et al., 1999) and supports the need for future studies to utilize oximeter's with optode distances of at least 5 cm.

A continuous wave (CW) NIRS oximeter was the method of choice for all of the studies we analyzed, and a limitation to the studies was the inability to quantify changes in cerebral oxygenation in absolute units. Newer NIRS technology such as time resolved spectroscopy or phase modulation spectroscopy promise the ability to provide an absolute value of the chromophore concentrations (Fantini et al., 1995). Several limitations of most of the NIRS devices used in the studies we reviewed must be taken into account such as interference of skull and meninges, contribution of scalp blood flow to changes in NIRS signal, and interpretations of concurrent changes in flow and volume (Ferrari et al., 2004). Cerebral hemoglobin is present in arterioles, capillaries and venules and tissue oxygenation is determined by arterial oxygen content and hematocrit, as well as by blood flow. Subsequently, changes in cerebral O2Hb and tHb measured by NIRS are not direct measures of cerebral perfusion alone (Ide and Secher, 2000). Accurate quantification of NIRS signals will be an important advance in the study of cerebral oxygenation during exercise because it will allow better comparisons between subjects with different pigmentation and skull thicknesses. Studies also are needed that use instruments with more regional head coverage. The choice by investigators in the studies we reviewed to measure hemodynamic changes in the frontal cortex was likely because of poor discrimination between cerebral and extracerebral tissue (e.g, hair follicles) by certain CW NIRS devices.

The predominant application of NIRS only to the left frontal cortex (usually between areas F1 and F6 of the international 10–20 system) in the extant literature weakens the conclusions that can be drawn about brain responses during exercise. It is undoubtedly the case that neural circuits consisting of multiple cortical regions act in concert with sub-cortical areas to regulate brain function and performance during sub-maximal and exhaustive exertion. A recent study that used multichannel NIRS during incremental leg cycling reported patterns of cerebral oxygenation and deoxygenation similar to those we summarized here for prefrontal cortex, as well as for pre-motor and motor cortexes (Subudhi et al., 2009). New systematic reviews using similar meta-analytic procedures will be needed after enough studies accumulate that use the newer technologies.

4.6. Implications for the study of brain function

It is important to consider how NIRS can be applied during exercise to advance our understanding of brain function beyond its role in limiting exercise performance (Nithianantharajah and Hannan, 2009; Stein et al., 2007). Evidence from prospective observational studies and randomized controlled trials suggests that regular physical activity or exercise training delay the onset of dementia and cognitive decline associated with aging, improve aspects of cognitive function or reduce symptoms of people diagnosed with Alzheimer's disease and other dementias, and have moderate effects for improving performance by healthy youths and older adults on several types of cognitive tasks, especially executive processing tasks (Tomporowski et al., 2008; Colcombe and Kramer, 2003; Hamer and Chida, 2009; Heyn et al., 2004; Physical Activity Guidelines Advisory Committee, 2008). Executive processing includes attention control, response inhibition, rule discovery, and working memory. It is mainly regulated by neural activity in the prefrontal cortices of the brain, areas that are further modulated by activity in the temporal and parietal cortices, the hippocampus, and several other brain areas involved with motivated behavior (Royall et al., 2002). The cumulative evidence in humans also indicates that a single session of acute exercise typically has small but positive effects on several types of cognitive performance (Lambourne and Tomporowski, 2010; Sibley and Etnier, 2003; Tomporowski, 2003) that do not uniformly depend upon cardio-respiratory fitness (Colcombe et al., 2004; Etnier et al., 2006).

Some plausible mechanisms that might explain enhanced cognitive function in response to exercise include enhancements in neurotransmitter systems that support attention and learning, neuronal plasticity, and brain blood flow (Dishman et al., 2006; van Praag, 2008). In a study of older adults without dementia, higher hippocampal volume partially mediated the relationship between higher fitness levels and enhanced spatial memory (Erickson et al., 2009). In a study of patients with early-stage Alzheimer's disease (Honea et al., 2009), there was a significant positive correlation of fitness with parietal and medial temporal cortical volume that was not observed in older adults without dementia.

Whether brain neural plasticity associated with physical activity depends on, or determines, changes in cerebral vascular responses and adaptations is as yet unclear. The anatomic location of brain changes associated with exercise also is not fully established. Early rat studies reported that acute increases in blood flow during treadmill running (Vissing et al., 1996) and adaptations in oxidative capacity after chronic wheel running (McCloskey et al., 2001) were mainly restricted to brain regions associated more with sensory processing and motor control than with cognition. Recent studies indicate that aerobic exercise training increases vascular density in the primary motor cortex and the rate of learning in monkeys (Rhyu et al., 2010) and cerebral blood volume and short-term memory in humans (Pereira et al., 2007). Exercise may also affect neural plasticity and function in other brain regions involved with cognition. In one study of fitness training, older adults had lower blood flow in the anterior cingulate cortex and better performance during an error-detection executive function task (Colcombe et al., 2004). Neuroimaging research suggests that cerebral white matter is decreased in older adults, especially in the prefrontal regions, and mediates age-related differences in cognitive function (Madden et al., 2009). A recent cross-sectional study found that aerobic fitness was related to greater white matter integrity in the cingulum (which projects from the cingulate cortex to the entorhinal cortex, the main neural input to the hippocampus), but not the prefrontal brain regions, in both young and old adults who had no neurological impairment (Marks et al., 2007). Aerobically active older adults also have less vessel tortuosity and an increased number of small vessels compared with less active subjects, which might contribute to cerebral white matter integrity (Bullitt et al., 2009).

Whether exercise induces altered blood flow and vascular changes that improve neural structure and function or whether exercise-induced changes in neural structure result in altered cerebrovascular responses are testable hypotheses. They can be explored in part by the use of NIRS in combination with evidence from other neural imaging modalities to provide descriptions of brain activation during serial episodes of exercise and their acute and accumulated effects on neural plasticity, cerebral vascular responses, and cognitive performance. Most studies of brain blood flow during acute exercise have been conducted under extreme conditions to understand limits to performance and central fatigue rather than cognitive function (Nybo and Nielsen, 2001; Nybo and Secher, 2004). A few studies that examined cognition during moderately intense or exhaustive exercise reported an enhancement of performance on decision-making tasks (Arcelin et al., 1998; Davranche and Audiffren, 2004; Paas and Adam, 1991) or an impairment of performance on perceptual (Paas and Adam, 1991) and executive control (Dietrich and Sparling, 2004) tasks. The cumulative evidence, indicates that performance on most cognitive tasks is impaired during exercise of short duration (i.e., 20 min or less), but performance during exercise is enhanced on tasks that involve rapid decisions and automatic behaviors (Lambourne and Tomporowski, 2010).

According to classic theory, the information processing system has limited capacity (Nithianantharajah and Hannan, 2009), so resources allocated to executing exercise would not be available for cognitive processing. The transient hypo-frontality hypothesis proposes that this reallocation of resources results in the temporary inhibition of neural networks that are minimally involved with movement (e.g., frontal brain) (Dietrich, 2003). Thus, processes depending on the frontal brain (i.e., executive control processes) would be impaired during exercise. However, in contrast to the hypo-frontality hypothesis, cognitive impairment during the dual tasks of interference control and cycling exercise has been accompanied by increased, rather than decreased, activation of neuro-electric systems of attention and information processing (Pontifex and Hillman, 2007). Those results suggest increased recruitment, or dis-inhibition, of neural resources indicative of inefficiency of executive control processing during exercise. Use of NIRS during dual cognitive processing tasks during or after exercise could help clarify anterior prefrontal function and limits of human decision-making (Koechlin and Hyafil, 2007; Charron and Koechlin, 2010), especially in response to incremental physical exertion.

In addition, research on attention and executive cognitive functions such as working memory has revealed the importance of understanding dissociations between tonic and phasic changes in alpha and theta oscillatory frequencies measured by electroenceophalography, especially in anterior–posterior neural circuits (Klimesch et al., 2008) that receive thalamocortical inputs (Hughes and Crunelli, 2005; Hughes et al., 2008). Recent findings suggest that theta oscillatory activity accounts in part for feelings of increased energy after acute exercise (Dishman et al., 2010). Activation of afferent input from carotid and cardiopulmonary baroreceptors into cardiovascular centers in the brain stem is alerting and increases indices of arousal, including hippocampal theta activity and activity in the insular cortex (Morgane et al., 2005; Spyer, 1989). It is plausible that brain cortical systems are altered generally in response to the increased metabolic arousal of physical exertion and the regulation of physical fatigue by the brain (Crabbe and Dishman, 2004; Magnie et al., 2000; Nielsen et al., 2001a; Nybo and Nielsen, 2001; Nybo and Secher, 2004; Pfaff, 2006). The extent to which cortico-thalamic input and associated neurocircuity are regulated and/or modified by varying intensities of exercise would, therefore, be a valuable avenue to pursue in subsequent NIRS research using multiple imaging modalities (e.g., Dale and Halgren, 2001; Hargreaves, 2008; Hiura et al., 2010) to more fully elucidate how anterior and posterior cortical brain activity during physical activity synergizes with sub-cortical structures to modulate mood or cognitive performance.

5. Estimated effects and critical sample sizes

Our analysis provides quantitative estimates of the effects that exercise has on cerebral oxygenation and blood volume under several conditions. This permits estimates of sample sizes needed to reject a null hypothesis for future studies that investigate several remaining questions about brain blood flow and oxygenation or deoxygenation during moderate-to-exhaustive exercise in a healthy population without known heart or lung diseases. *A priori* estimates of critical sample sizes in each level of effect moderators were provided in Table 2 for effects exceeding 0.20 SD (Cohen, 1988).

The standard deviation of change used in the statistical test of mean differences between two correlated scores provides an effect size (Cohen's *dz*) that is standardized relative to the variance of the difference scores rather than the distribution of the dependent variable. Adjusting the standard deviation of change by the correlation (r) between the two scores gives an estimate of the pooled standard deviation of the dependent variable (Cohen's d) (Lipsey and Wilson, 2001). Effects expressed in standardized units of the dependent variable can then be judged according to their likely statistical and clinical impact in a population. Only 3 of the studies we located provided r (Bhambhani et al., 2006; Koike et al., 2004b; Subudhi et al., 2007). Using values of $r = 0.80$ or 0.90, respectively, the weighted means (95% CI) of Cohen's d estimated from the effects (*dz*) we derived from the studies retrieved in this review would be: Healthy people: cerebral oxygenation (O_2Hb, O_2Hbdiff, SCO_2) ($d = 0.64$ (0.46–0.83) or $d = 0.49$ (0.34–0.63), dHb $d = 0.80$ (0.38–1.22) or $d = 0.58$ (0.29–0.88), tHb $d = 0.97$ (0.58–1.37) or $d = 0.73$ (0.38–1.08); Patients: cerebral oxygenation $d = -0.13$ (-0.19 to 0.46) or $d = -0.11$ (-0.26 to 0.04), dHb $d = 0.11$ (-0.32 to 0.55) or $d = 0.08$ (-0.22 to 0.39), tHb $d = 0.19$ (-0.14 to 0.52) or $d = 0.13$ (-0.19 to 0.46). These effects are

conventionally judged as statistically moderate-to-large for healthy people and small for patients (Cohen, 1988), but their practical or clinical impact remains to be determined according to performance or health outcomes.

6. Conclusions

Since its initial application (Jobsis, 1977), NIRS has been used as a practical indicator of cerebral oxygenation and hemodynamic change during sub-maximal (Ide et al., 1999) and maximal exercise (e.g., Bhambhani et al., 2007; Gonzalez-Alonso et al., 2004; Subudhi et al., 2007; Timinkul et al., 2008). This systematic review provides quantitative estimates of the quadratic response of cerebral oxygenation to increments of exercise intensity, showing increases from low-to-hard intensities followed by a plateau or decline toward baseline at very hard, maximal intensities. Responses were modified by training status. The plateau in cerebral oxygen levels concurrent with increasing dHb and blood volume observed at very hard, exhaustive intensities of exercise in aerobically trained people is relevant for integrative physiology models developed to explain how reduced central drive could limit maximal exercise capacity. The lower O_2Hb, dHb, and blood volume attained at very hard intensities by untrained, less fit people are consistent with reduced cerebral blood flow. The results suggest testable hypotheses about mechanisms that regulate cerebral blood flow and metabolism during incremental, sub-maximal and maximal exercise. At increments from low-to-hard intensities, TOI results were not coherent with increases in O_2Hb and dHb, suggesting that the interpretation of TOI as an index of cerebral oxygen saturation during sub-maximal exercise requires clarification. There were not enough studies that used TOI or SCO_2 to draw conclusions about differences in oxygen saturation at maximal exercise according to training status. Elevations seen in measures of O_2Hb during moderate and hard intensities of exercise are not consistent with the 'hypofrontality' hypothesis of cognitive and affective responses to sub-maximal exercise. The effect sizes derived in the review can guide future experiments by estimating sample sizes needed to detect significant change in oxygenation, dHb, and blood volume at varying exercise intensities in healthy participants. Small-to-moderate reductions or no changes in brain oxygen and dHb during moderate or hard intensities of exercise were reported in the few studies of people diagnosed with heart and lung diseases. As NIRS technology continues to improve, considerations of optode distance and location, and reconsideration of and use of quantifiable light signals will expand the information that can be obtained using NIRS during and after exercise to understand cortical brain function and its role in human performance and health, especially when NIRS is used with other neuroimaging measures concurrent with controlled manipulations of the brain (e.g., Rasmussen et al., 2010).

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