The dynamics of brain activity during aerobic exercise until exhaustion

- a NIRS study

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Abstract

Aim: the main aim of this study was to investigate how the relation between the cerebral oxygenation (COX) of the prefrontal cortex (PFC) and performance on prefrontal-dependent cognitive tasks, changes during prolonged, high intensity (HI) exercise until exhaustion. An additional aim was to see if the changes occuring in the PFC are exclusive to this region or if they are similar in other regions of the brain.

Method: Three sessions were conducted on an ergometer bicycle with a screen for cognitive tasks: 1. Learning session for cognitive tasks (Eriksen Flanker (EF) and N-back) and a VO2max test, determine first ventilatory threshold. 2. One session with HI exercise and cognitive tasks. 3. One session with low intensity (LI) exercise and cognitive tasks. The second and third session included measuring the COX during exercise, as well as recording baseline values before onset of exercise, using a near infrared spectroscopy (NIRS) system. Regions measured were occipital cortex (OC), motor cortex (MC), and medial-, dorsolateral (DL)- and right inferior (RI) PFC. Defined two periods; initial and ending, in order to compare start and end of exercise.

Results: Significant difference between the COX of the MC, and the medial PFC and DLPFC, and between the MC and the OC, was found, as well as between regions within the PFC. The O_2Hb values of the medial- and DLPFC both increased from baseline, but were significantly higher in LI than in HI exercise, and in the ending than in initial period. In HI exercise, the reaction time (RT) on the EF task was significantly faster in the ending period, without change in accuracy. No significant changes were found for LI exercise, or for the N-back task.

Conclusion: The findings in this study points to the need of separating between different regions within the brain, as well as between regions within the PFC, when talking about the dynamics of the COX during exercise. This study showed that the dynamical pattern for performance on prefrontal dependent cognitive tasks differed from the pattern of O_2Hb in the regions where these tasks are facilitated, and leaves the link between the COX and cognition uncertain. Different factors like duration and intensity of exercise seem to affect both the COX, and more locally in the PFC, in addition to influencing the complex relation between the COX of the PFC and performance on cognitive tasks. This points to a need for more extensive recording of the COX of the MC, the pre-MC and the PFC, in order to have a more informed image of the complex interaction between the different regions, and between the implicit and explicit system during exercise.

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Abbrevations

COX - cerebral oxygenation

PFC – prefrontal cortex

HI – high intensity

LI – low intensity

EF – Eriksen Flanker

RT – reaction time

NIRS – near infrared spectroscopy

OC – occipital cortex

MC – motor cortex

DLPFC – dorsolateral prefrontal cortex

RIPFC – right inferior prefrontal cortex

O_2Hb – oxygenated hemoglobin

HHb – deoxygenated hemoglobin

THb – total hemoglobin

RAH – reticular activating hypofrontality

RPE – rated perceived exertion

CONTENT

1. Introduction

Sustained attention over a prolonged period of time during physical performance is necessary in many sports, like for example skiing, orientation and cycling, and in professions like the military. Physical performance in such prolonged high-intensity (HI) exercise is limited by fatigue, but there are uncertainties about what the main limiting factors are (1). There is a lot of research and information on the neuromuscular responses to acute prolonged exercise maintained until exhaustion, but less on the cognitive responses. The brain has finite and limited resources and the hemodynamics of the brain have to change from rest to meet the needs of exercise (2). More information and knowledge about these changes, could give a greater understanding of the cerebral limiting factors for prolonged HI exercise.

Dietrich and Sparling (3) found evidence that some cognitive executive functions are impaired during acute exercise. This discovery elicited many theories from different scientists, but most of them only explained one or two aspects of the processes occurring in the brain during exercise. The Reticular Activating Hypofrontality theory (RAH) (2) attempts to describe all aspects, and states that there are two different and opposite processes taking place; one reticular activating process and one down-regulation process of the prefrontal cortex, which could lead to a state called hypofrontality. To understand these processes, it is important to distinguish between two different information-processing systems in the brain; the implicit and the explicit system. The explicit system mostly relies on structures located in the prefrontal cortex (PFC) and it is where all the cognitive, executive functions take place (2). This region is known to project to premotor areas, be involved in movement planning, decision making (4), working memory, conscious thoughts and emotions, guide social behavior and morality, and create self-awareness (5). The implicit system on the other hand is based on experience and skill, it is inaccessible to conscious awareness, and it can only be shown through task performance (2). The initiation and continuation of exercise activates arousal systems in the reticular formation, which then stimulate motor movements and increase attention to the task at hand in order to make movements more efficient. This requires that the movement is known, as a new movement pattern will have to be learned in the explicit system before it can be performed more automatically and fluent through the implicit system. From an evolutionary point of view the hypofrontality state is proposed as a mechanism for the brain to deal with the limited resources; by down-prioritizing the functions that is not absolutely necessary in a fight or flight situation (equivalent to exercise nowadays). By distinguishing the implicit and the explicit systems, it can contribute to explain how some cognitive functions can be enhanced and some impaired during exercise (2); if a movement pattern or cognitive task is familiar, it can possibly be facilitated through the implicit system and therefore be performed more efficiently, while more extensive prefrontal dependent tasks might be impaired because of the down-regulation of the PFC during exercise. There are however some controversies about whether or not the whole PFC can be described with such global theories, or if it should be distinguished between different regions within the PFC. Studies show that working memory tasks activate mainly the dorsolateral PFC (DLPFC) (6), while selective inhibition seems to activate the right inferior PFC (RIPFC) (7).

Near infrared spectroscopy (NIRS) is a non-invasive measurement of hemoglobin saturation and has during the last two decades, opened a lot of doors for recording brain activity during cognitive tasks and exercise in healthy people (8). It reflects the amount of oxygenated (O_2Hb), deoxygenated (HHb) and total hemoglobin (THb; the sum of O2Hb and HHb) in the area measured (8). Given its relatively strong ability to resist to movement artifacts, NIRS has become the most used method to probe neural activity during exercise, and it has also proved to be a good tool for examining cognitive effects of exercise in several studies (9, 10).

There are however large controversies about how the COX changes during exercise. Rupp et al. (11) found a different pattern in prolonged submaximal exercise, than the one described for maximal exercise (< 20 min) until exhaustion (12). Both these patterns differ from the one described in the RAH theory, and points to a complex interaction between COX and exercise.

Timinkul et al. (12) proposed that there are three phases of COX of the PFC during shorter (< 20 min) maximal exercise until exhaustion: a linear oxygenation at first, then hyper oxygenation until Respiratory Compensation Point (RCP), where a rapid desaturation takes places. This is supported by the findings in other studies using incremental exercise (13, 14), where changes happen approximately in line with these phases. Also, Rooks et al. (15), using an incremental protocol, found that the deoxygenation-process happens at an earlier stage for aerobically untrained than for trained individuals (throughout article, the expressions trained and untrained refers to aerobic fitness).

For prolonged submaximal exercise, there seems to be a more constant increase in oxygenation of the PFC, with no deoxygenation process before the end of exercise (11). One study (16) showed that Kenyan elite distance runners did not experience a deoxygenation of the PFC before the end of a maximal, self-paced 5 km run, although did have a deoxygenation of the PFC during an incremental test. Thus, changes in the COX of the PFC during prolonged exercise may contribute to performance limitation by impairing executive functions (e.g., decision to stop exercising) and central motor drive indirectly. Different factors like duration, intensity and fitness level of the subjects, seem to affect the COX of the PFC.

Suzuki et al. found that an incremental protocol could cause attention bias from the adaption to speed and possibly affect the NIRS signal (17), and the shorter duration might not give enough time for the subject to reach the state of hypofrontality, as duration is crucial (2). Most research is done with a shorter, incremental protocol, and there is a knowledge gap about how the COX changes during a prolonged (> 20 min), HI exercise until exhaustion, and how these changes affect prefrontal-dependent cognition.

This leads to the *main aim* of this study, which is to investigate how the relation between the COX of the PFC and performance on prefrontal-dependent cognitive tasks, changes during prolonged (> 20 min), HI exercise until exhaustion. An additional aim is to see if the changes happening in the PFC are exclusive to this region or if they are similar in other regions of the brain.

The hypothesis: based on previous studies, it is anticipated that in the first period of HI exercise, the COX in the PFC will increase from baseline, while right before exhaustion state occurs, the PFC will have a rapid deoxygenation and possibly the motor cortex will be more facilitated. It is further anticipated that the deoxygenation of the PFC towards end, will cause the response on the EF task to be faster, but less accurate, and the n-back task will have a higher error rate, due to the down-regulation of the PFC and therefore more facilitation through the implicit system.

2.0 Method

2.1 Participants

Sixteen participants were initially recruited but five participants dropped out of the study before completing all the experimental sessions for various reasons. The final sample of participants consisted of eleven aerobically untrained individuals (three females and eight males), students and employees at the sport faculty at the University of Sophia Antipolis. All of them provided written consent (according to the Helsinki declaration). The average ± standard deviation (SD) age, weight and height were 22.7 ± 4.5 years, 63.5 ± 9.0 kg and 174.2 ± 9.0 cm, respectively. Average VO_2max for all participants was 49.9 ±11.1, men 53.6 ± 9.1 and women 40.0 ± 10.9, respectively. In average they exercised for 3.9 ± 1.8 hours per week, with a wide variation of sports among the participants. The subjects could at all times withdraw from the project. The students received points in the school system for attending. Subjects were excluded if they had very thick hair, because that could affect the quality of the NIRS signals.

2.2 The ergometer bicycle and the EEG-cap

All sessions were performed on an ergometer bicycle (Brain-bike NeuroActive, recumbent bike, BE-7216, Taiwan) equipped with a screen for cognitive tests (Eprime 2.0 software) and buttons for left and right hand, with soft handlebars to support forearms. An EEG-cap was adapted with custom formed plastic pads to hold the NIRS optodes, and Cz reference from the electro-encephalic 10-20 international system were used to locate the medial PFC, DLPFC, RIPFC, motor cortex (MC) and the occipital cortex (OC).

Figure 1: Experimental set-up for the exercise and control conditions

2.3 Experimental procedure

The subjects participated in three sessions; the first session lasted approximately one hour and the second and third sessions approximately for two hours. All sessions were conducted at the same time of the day. The subjects were instructed to withstand from any vigorous exercise the day before, to have a good night sleep for at least 7 hours, and not to be affected by any psych stimulants (coffee, alcohol etc.) at the day of the test.

First session

The subjects were given the written consent form to read through and sign. They were weighed and answered questions about age, height and exercise status. Four blocks of 100 trials of each of the two cognitive tasks (Eriksen Flankers task (EF) and the N-back task) were conducted in order to avoid learning bias in the experimental sessions. They were instructed to focus on the reaction time (RT) in the EF test, and to focus more on answering correct in the N-back test. Learning criteria to be achieved was a less than 5% increase in performance from the previous test, and if it was higher; they had to take another test in order to achieve this criterion. After the cognitive tests, they adjusted the seat of the bike to sit comfortably with their feet on the pedals before a maximal oxygen consumption (VO_2max) test was conducted. The Polar system (Polar RS800CX, Polar Electro Oy, Kempele, Finland) was used to measure the heart rate (HR) during the exercise, and a USB stick was attached to the Fitmate Pro gas analyzer (COSMED, Miami, USA, validated by Nieman et al. (18)) to show the HR on the screen. The subjects wore a mask that was attached to the Fitmate Pro which recorded oxygen consumption ($ml.kg^{-1}.min^{-1}$) and ventilatory output ($L.min^{-1}$). Warm up was conducted at 70/80 watt (women and men, respectively) for four minutes, and then power was increased by 20 w per minute until exhaustion. Exhaustion was defined as a deliberate stop, or when the participant could no longer maintain a pedaling frequency above 50 rotations per minute (RPM) for over 10 seconds, despite excessive cheering. The VO_2max test was conducted at the same bike as the experimental sessions. Physiologists visually decided the first ventilatory threshold (VT1) for each participant by evaluating plots showing minute ventilation (VE) over time and minute ventilation over oxygen consumption (VO_2) over time.

Second and third sessions

The second and third sessions were counterbalanced to avoid order effect bias.

Second session, high-intensity (HI) exercise

The participants exercised at a watt level equivalent to their individual VT1. A lactate test was performed using the Lactate Pro LT 1710, and they adjusted the seat and back-support BrainBike to their comfort. They were explained how the BORG-scale worked (19)(a rating of perceived fatigue level, ranging from 6 to 20, with 20 being the highest level of fatigue). One test with 100 trials for the two cognitive tests was conducted in order for the participants to recall the tests from the learning session and avoid learning bias during exercise. The cap with the NIRS optodes were attached to the subjects head, and a measuring band was used to adjust the cap and the location of the optodes. The program Oxysoft 2 was turned on to check the signals of the different channels, and the optodes were adjusted as needed (remove hair or tighten the cap). When the signals were acceptable, the participants were instructed to sit still for two minutes while the baseline values for the COX were measured. The BrainBike was set to constant power before the warm up (70/80 w for women and men, respectively). They performed the warm up for 5 minutes and then intensity was progressively increased in a two-minute window to the pre-determined watt level (equivalent to individual VT1) for the exercise. At seven minutes, the NIRS trigger for task A was started at the same time as the first cognitive task was started. They performed the two cognitive tasks (about 100 trials for the EF task and 60 trials for the n-back, the order was counterbalanced between participants), followed by one minute without a cognitive task, but still pedaling. During this period, they were asked how they felt on the rating's perceived exertion scale (BORG scale). This order was repeated until exhaustion, while giving the participant half a glass of water every other pause (voluntary) of the cognitive tests. Voluntary exhaustion was defined as a deliberate stop from the participant, with a subjective feeling of fatigue equivalent to the higher end of the BORG scale. A lactate sample was conducted immediately after exercise.

Third session, low-intensity (LI) exercise (control)

The protocol was the same for the LI exercise session (control), except that they pedaled at 30 and 40 w for women and men respectively, and there were no warm up.

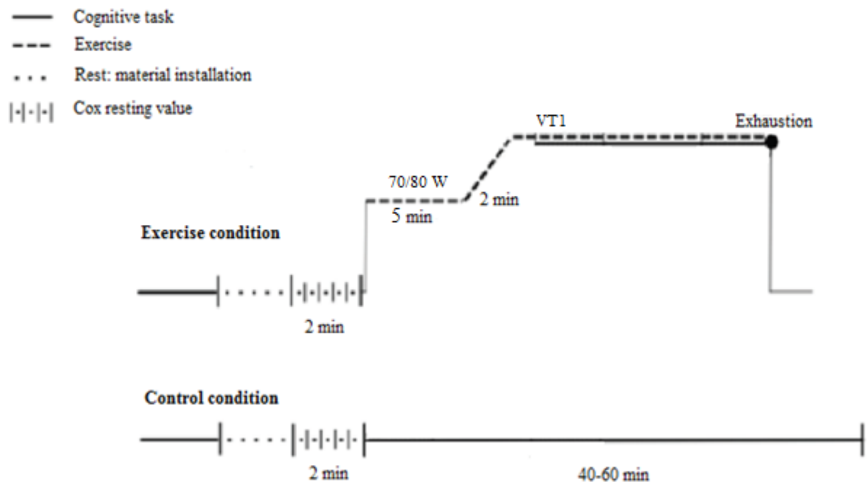

Figure 2: Protocol for HI exercise and LI exercise (control) session. 100 trials of one of each cognitive task were conducted, followed by material installation, and two minutes of recording baseline values. HI exercise session; a warm up at 70/80w (women/men respectively), followed by a two minutes increase, and then exercise at intensity equivalent to individual VT1 until volitional exhaustion. In LI exercise session (control) they pedaled at 30/40w (women/men, respectively) for approximately the same duration as HI exercise session.

2.4 The two cognitive tasks

The Eriksen Flanker task tests reaction time (RT) and accuracy, by having the participant press right or left key as fast as possible, in the same direction as the arrow in the middle. Congruent trials are when all the arrows point in the same direction, and incongruent are when the middle arrow points in a different direction than the surrounding arrows. We used a modified version, which includes more arrows, and the image can pop up at different locations of the screen. The participants were asked to answer as quickly as possible, and will have to selectively inhibit the reflex of pressing the same direction as the other arrows in the incongruent trials (20).

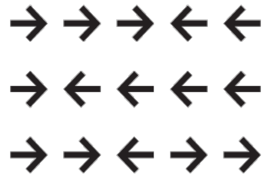

Figure 3: Eriksen Flanker task, showing an incongruent test

The N-back task tests working memory (WM), and we used the 2-back version. The participant has an image in front of them for approximately two seconds, and they have to remember if it is the same image as the one two times back, and either press left (not the same image) or right (same image as two times back) button to answer. The calculation of a *d*-prime value takes into account how many hits (correct hits) and how many false alarms (presses for the same image, but it is different) there is, thus correcting for individual response bias (21).

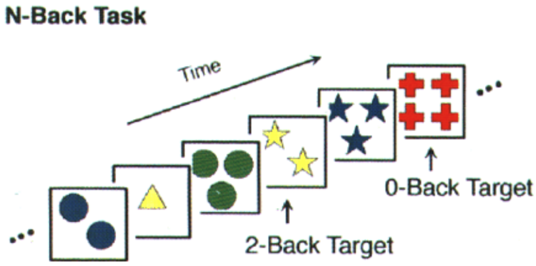

Figure 4: N-back task, only one image showing at the time. The participant have to remember the image showing two times back

2.5 Near Infrared Spectroscopy

The NIRS system (Oxymon Mk III, Artinis Medical Systems, Portalite, Netherlands) consisted of 5 channels (5 x 1, split channels), and the concentrations were recorded from two pathlengths (773 and 853 nm), sampled at 10 hz, and emitted by five sources (inter-optodes distances on the PFC; 4 cm, and for the MC and OC: 3 cm). NIRS functioning principle is based on the measurement of infrared light reflected after scattering within tissue, and with different absorption properties of the hemoglobin, the system can detect and separate between oxygenated (O_2Hb) and deoxygenated (HHb) hemoglobin(8).

The exact locations for the five channels according to the SENIAM 10-5 system with their approximately MNI coordinates (22):

Channel 1 – medial PFC:	AF2h 10 66 26
Channel 2 – DLPFC:	F6h 49 42 23
Channel 3 – RIPFC:	FFT8h 58 25 5
Channel 4 – MC:	C2 30 -14 71
Channel 5 – OC:	O2 22 -102 7

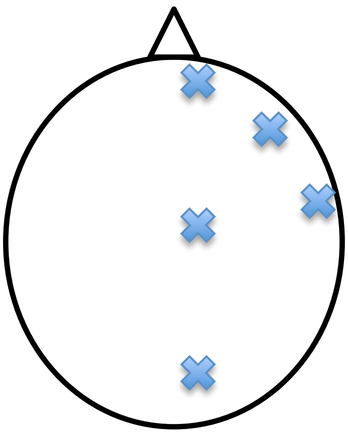
Figure 5: Localization of the channels.From left, starting from the nose; ch. 1, ch. 2, ch.3 on the PFC. In the middle: ch. 4 on the MC, and on the bottom: ch. 5 on the OC

It was anticipated that channel 1 would be most active during the period without any cognitive tasks, channel 2 during the EF-task (inhibition of the flankers, incongruent trials), and channel 3 during the n-back task (WM). Channel 4 records the MC and channel 5 records the OC (reference).

2.6 Data processing and analysis

Objective fatigue

Significance level and values from pre to post measurements of lactate was checked using paired-samples t-test.

In order to compare the first and the last phase of prolonged maximal exercise, one *initial* period consisting of the two first cognitive tasks performed in each condition, and one *ending* period consisting of the two last cognitive tasks performed in each condition was defined both for the COX recordings, as well as for the cognitive tasks.

Cognitive test performance

Eriksen Flanker test: significance level and mean values for differences in RT and accuracy between conditions (HI and LI), periods (initial and ending) and the congruency of the tests (congruent or incongruent) were checked using a non-parametric test (2 related samples K).

N-back test: Significance level and values for main effects of conditions and periods on the *d*-prime value, and interactions between conditions and periods, were checked using linear mixed model.

Cerebral oxygenation

Data processing*:* A low pass filter (0.1 Hz) was applied in the OxySoft 2 program in order to remove physiological influences on the signal. In excel, the values were normalized to baseline values, and they are shown as change from baseline. No significant difference in oxygenation between the two tasks was observed, and therefore they were merged, and further analyses are done for the combined tasks (The initial and ending periods consist of one of each of the cognitive tasks). Control condition results were adapted to retain the same duration as in the exercise condition, as close as possible regarding the counterbalancing of the two conditions.

Analysis*:* Significance level for main effects of conditions, periods and channels were checked for using linear mixed model. Significance levels were also checked for the interactions between: conditions, channels and periods; channels and periods; channels and conditions; periods and conditions. Significant main effects and interactions were further explored using Post-Hoc tests (EMMEANS, Bonferroni) and split file in linear mixed model, in order to compare means from the interactions, and investigate differences between factors.

All analyses were done in SPSS (IBM® SPSS® Statistics 21).

3.0 Results

All included participants completed the protocol, however in many cases the desired duration of over 40 min was not met. The mean duration for all participants was 32.5 ± 19.8 min, and the mean number of rounds for the two cognitive tests was 6.2 ± 3.8. Mean rated perceived exertion (RPE, BORG scale) when they ended sessions were significantly higher for HI exercise (19.5 ± 0.9) than for LI control (9.5 ± 3.2) ($P = .003$).

3.1 Cycling test performance

Significant difference was observed between the two post-measurements ($P = .003$), and between pre- and post-measurements in exercise condition ($P = .003$), while no significant differences were observed between the two pre-measurements ($P > 0.05$), or between pre- and post-measurements in control condition ($P > 0.05$).

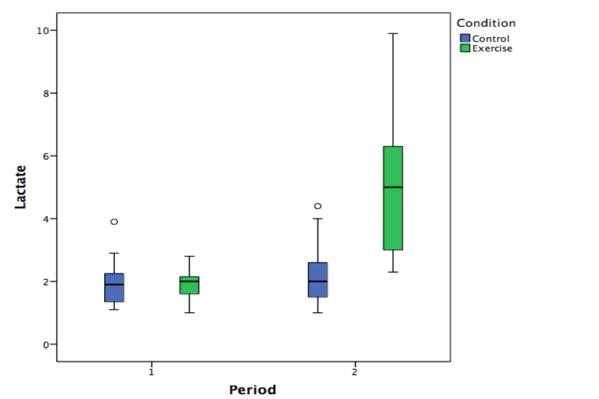

Figure 6: Mean values for lactate, pre and post measurements in LI (blue) and HI (green) exercise.

3.2 Cognitive test performance

Eriksen Flanker task

In both conditions and in both periods, RT was significantly faster for congruent than for incongruent tests (mean difference: .057 sec, $P < .003$), and accuracy was significantly better for congruent than for incongruent trials (mean values of 98.2% vs 84.7%, respectively, $P < .008$). In the exercise condition, RT tended to be faster for most subjects in the ending period than in the initial period (congruent, $P = .013$, incongruent, $P = .09$ (trend)), while no other significant differences were observed for accuracy ($P > .21$). No significant differences for RT or accuracy were observed between the two conditions in the initial period ($P > .21$, and $P > .49$, respectively), or between initial and ending period in control condition ($P > .37$, and $P > .73$, respectively).

N-back task

The mean *d*-prime for the group throughout both conditions and periods was 1.9 ± 1.8. Using linear mixed model, no significant main effects of, or interactions between, periods and conditions were observed ($P > .42$).

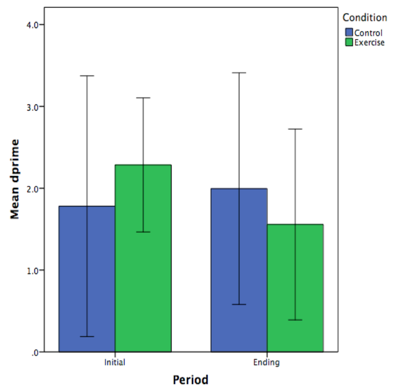

Figure 7: Mean (± stddev) *d*-prime from N-back test showing values from the two periods and the two conditions

3.3 Cerebral oxygenation

Table 1 shows that significant main effects of condition and period on O_2Hb and THb were observed, and channel had a significant main effect on all three values of hemoglobin. A significant interaction was found between condition and channel; and channel and period (trend for HHb) for both O_2Hb and THb. For condition, channel and period there was no significant interaction, although a trend in THb. No other significant main effects or interactions were found.

Table 1 shows the p-values for main effects of, and interactions between the conditions, periods, and channels for all three values of hemoglobin

Main effects	**O_2Hb (µmol.cm)**	**HHb (µmol.cm)**	**THb (µmol.cm)**
Condition (control/exercise)	.05*	.18	.05*
Period (initial/ending)	.02*	.70	.03*
Channel (1-5)	.00*	.00*	.00*
Interactions			
Condition * channel	.00*	.13	.00*
Channel * period	.03*	.09**	.01*
Condition * period	.89	.84	.96
Condition * channel * period	.15	.35	.09**

Level of significance set to $P \leq .05$.
* = significant at .05 level, ** = trend

To investigate which channels had different O_2Hb values from each other, a post-hoc pairwise comparison was used in the linear mixed model analysis:

Ch. 1 differed from: 3 (2.6, $P < .01$) and 4 (2.7, $P < .01$)

Ch. 2 differed from: 3 (2.2, $P = .02$) and 4 (2.2, $P = .02$)

Ch. 3 differed from: 1 (-2.6, $P < .01$) and 2 (-2.2, $P = .02$) and 5 (-1.8, $P = .08$ (trend))

Ch. 4 differed from: 1 (-2.7, $P = .00$) and 2 (-2.2, $P = .02$) and 5 (-1.9, $P = .07$ (trend))

Ch. 5 differed from: 3 (1.8, $P = .08$ (trend)) and 4 (1.9, $P = .07$ (trend))

Thus, channel 1 and 2 have significantly higher O_2Hb values than channel 3 and 4, and channel 5 has a trend for higher O_2Hb values than channel 3 and 4. Channel 1, 2 and 5 were not significantly different from each other, however there seems to be a difference in the pattern of oxygenation (from table 2 and 3), although not significant. Channel 3 and 4 were not significantly different from each other.

Table 2 shows that for the interaction between conditions and channels, the increase in both THb and O_2Hb values from baseline is significantly higher in control than in exercise for channel 1 and 2, but there is also an increase in exercise condition. For channel 5 there is a higher increase in exercise condition, but the difference from control is not significant. Only small differences are observed for channel 3 and 4, where there are small decreases from baseline, but the change between conditions is not significant.

Table 2: An overview of the mean values for O_2Hb and THb (±std-error) from the significant interaction between condition and channel, and the differences between the two conditions, shown with p-values

Channel	**O_2Hb** (±std-error)			**THb** (±std-error)		
	Base to control	Base to exercise	Difference (exercise-control)	Base to control	Base to exercise	Difference (exercise-control)
1	4.0 ± 0.7	0.9 ± 0.7	-3.1 (P = .01)	4.9 ± 0.9	1.2 ± 0.9	-3.7 (P = .01)
2	3.4 ± 0.7	0.5 ± 0.7	-2.9 (P < .001)	5.1 ± 0.9	1.3 ± 0.9	-3.8 (P = .00)
3	-0.4 ± 0.7	-0.0 ± 0.7	0.4 (P > .10)	-0.3 ± 0.9	0.3 ± 0.9	0.6 (P > .10)
4	-0.1 ± 0.7	-0.5 ± 0.7	-0.4 (P > .10)	-0.1 ± 0.9	-1.0 ± 0.9	1.1 (P > .10)
5	0.7 ± 0.7	2.4 ± 0.7	1.7 (P > .10)	0.9 ± 0.9	3.2 ± 0.9	2.3 (P > .10)

Level of significance set to $P \leq .05$

Table 3 shows that for the interaction between period and channel, the increase in O_2Hb values from baseline was significantly higher in ending than initial period for channel 1 and 2. For channel 5 it was also slightly higher in ending than in initial, but the difference was not significant. Channel 3 and 4 showed a decrease to right below baseline values for ending period, but the small difference from initial period was not significant. For THb, changes in channel 1 and 2 were similar as for O_2Hb, but for channel 4, the ending period had a greater reduction (below baseline) than in initial, though the difference was not significant.

Table 3: An overview of the mean values for O_2Hb and THb (±std-error) from the significant interaction between period and channel, and the differences between the two conditions, shown with p-values

Channel	**O_2Hb** (±std-error)			**THb** (±std-error)		
	Base to initial	Base to ending	Difference (ending – initial)	Base to initial	Base to ending	Difference (ending – initial)
1	1.2 ± 0.7	3.7 ± 0.7	2.5 (P = .03)	1.2 ± 0.9	4.9 ± 0.9	3.7 (P = .01)
2	0.5 ± 0.7	3.4 ± 0.7	2.9 (P = .00)	1.3 ± 0.9	5.0 ± 0.9	3.7 (P = .00)
3	-0.2 ± 0.7	-0.3 ± 0.7	-0.1 (P > .10)	0.0 ± 0.9	0.0 ± 0.9	0.0 (P > .10)
4	0.0 ± 0.7	-0.6 ± 0.7	-0.6 (P > .10)	0.0 ± 0.9	-1.1 ± 0.9	-1.1 (P > .10)
5	1.4 ± 0.7	1.8 ± 0.7	0.4 (P > .10)	2.1 ± 0.9	1.9 ± 0.9	-0.2 (P > .10)

Level of significance set to $P \leq .05$

Figure 8 shows the three values for hemoglobin in the five channels measured during initial and ending periods, in control and exercise, respectively.

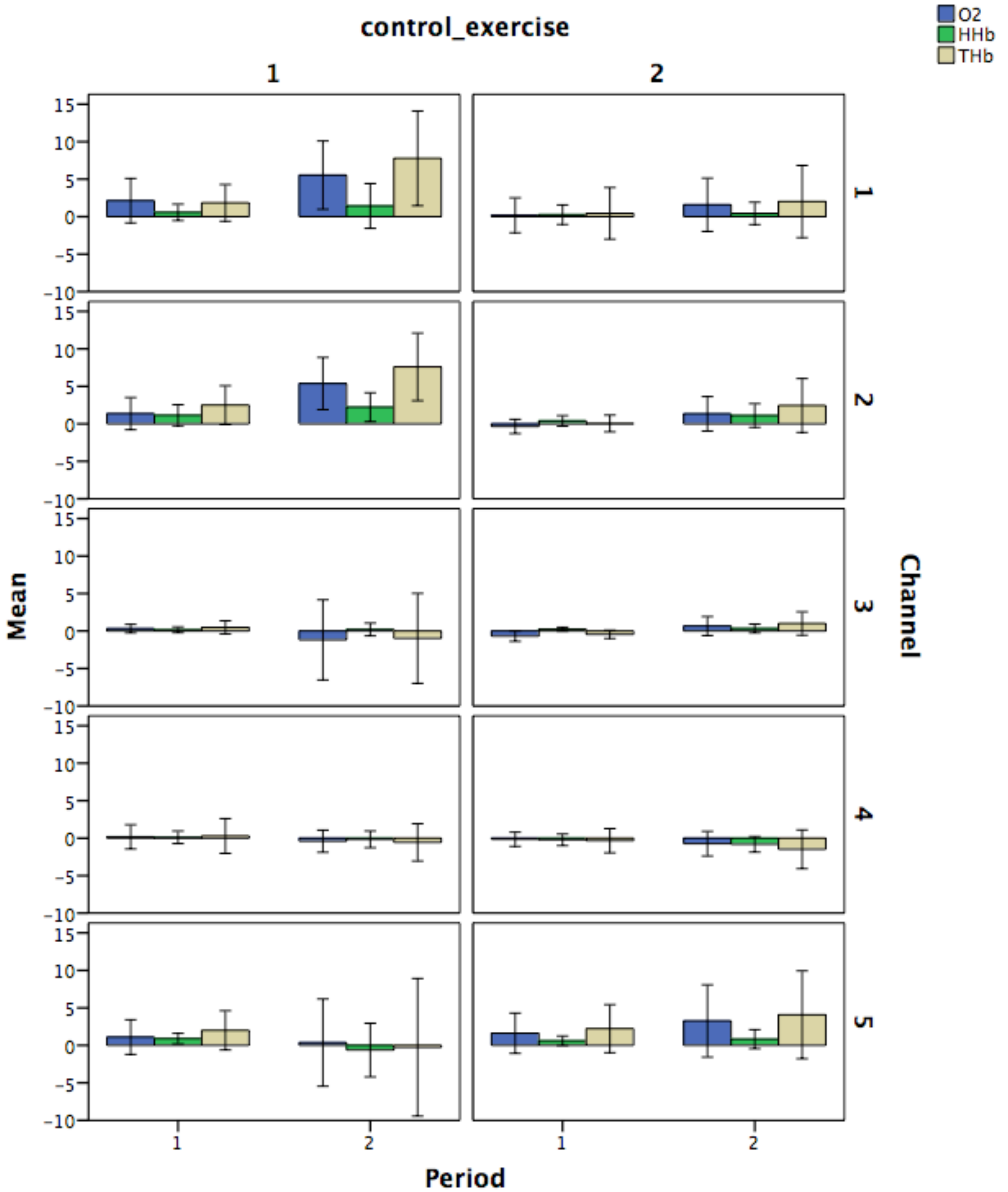

Figure 8: Mean ± stddev (0.95) hemoglobin values in the two periods during exercise and control condition, shown for the three channels from the PFC, from initial (1) to ending (2) period.

4.0 Discussion

The main aim of this study was to investigate how the relation between the cerebral oxygenation (COX) of the prefrontal cortex (PFC) and performance on prefrontal-dependent cognitive tasks changes during prolonged, high intensity (HI) exercise until exhaustion. An additional aim was to see if the changes happening in the PFC are exclusive to this region or if they are similar in other regions of the brain.

4.1 Main findings

Cycling: Neuromuscular fatigue in the HI exercise condition was attained according to subjective RPE, as well as metabolic muscle fatigue (lactate) (23), while LI exercise was considered as having no significant fatigue. The mean duration of cycling was 32.5 minutes.

Cognition: For the Eriksen Flanker task, in HI exercise, RT was significantly faster in ending than in initial period for most participants, with no significant changes in accuracy. No significant changes for RT or accuracy were observed between initial and ending period in LI exercise, or between the two conditions in the initial period. For the n-back task, no significant changes were observed between the two conditions or periods.

Cerebral oxygenation: For O_2Hb and THb there was a significant main effect of condition, period and channel, while for HHb only a significant effect of channel was observed. For O_2Hb and THb, a significant interaction between channel and period; and channel and condition was observed. For both these interactions, O_2Hb and THb had a similar pattern; for channel-condition interaction, increases from baseline were observed in medial and DLPFC, with a significantly higher increase for LI than for HI exercise. For OC there was a higher increase for HI exercise than for LI, but the difference was not significant. For channel x period interaction, increases from baseline to both initial and ending period were observed in medial and DLPFC, with a significantly higher increase in ending. There were also small decreases from baseline in RIPFC and MC, however the difference between periods was not significant. There was a small but insignificant increase for the occipital cortex from initial to ending period.

The COX of the medial PFC, the DLPFC and the OC were not significantly different from each other, although from the interactions in table 2 and 3 in addition to visually from figure 8, a different pattern for the COX in the OC was observed. The COX values for the medial PFC and the DLPFC were not significantly different from each other, and neither were values for the RIPFC and the MC. The medial and the DLPFC had significantly higher O_2Hb values than the RIPFC and the MC, and the OC had a trend for slightly higher O_2Hb values than the RIPFC and the MC.

4.2 Regional differences for the COX during exercise

There are large controversies about whether or not different regions of the brain respond similarly to exercise. Results from previously studies points toward a need for separation between the COX changes occurring during shorter maximal (< 20 min) (12) and changes occurring during prolonged submaximal exercise (11). Both a hyperoxygenation followed by a deoxygentation of the PFC right before exhaustion (13-15), and a continuous deoxygenation of the PFC from start to end (24) in shorter maximal exercise has been found, and points toward the possibility that this region is involved in the decision to stop exercising. However, are the changes in COX similar in other regions as well, or are they exclusive to the PFC? Different responses between the MC and the PFC have occurred both in prolonged, fatiguing exercise (11), and in shorter maximal exercise (< 20 min) (14). In one study using prolonged submaximal exercise (11), a hyperoxygenation of the PFC and a significantly decrease of O_2Hb in the MC occurred simultaneously. The results from the current study showed that there was a higher O_2Hb value for the medial PFC and the DLPFC than of the MC, in both HI and LI exercise and in both periods, but there was no significant difference in oxygenation between the MC and the RIPFC. Thus, both in high and low intensity prolonged (>20 min) exercise, there seems to be different patterns for oxygenation of parts of the PFC and the MC. In addition, the COX pattern for the OC seems to be different from the other locations, although there were no statistical significant differences (see table 2 and 3, and figure 8). One study (25) found that the OC was unaffected during an incremental exercise until exhaustion.

These findings and the large variance in results from different studies, argues in favor of not having global theories applying for the whole brain when talking about cerebral limitations to exercise. Different factors like duration and intensity seem to affect the COX pattern of the different regions, but further research is needed in order to gain more insight in these differences, especially for prolonged fatiguing exercise (> 20 min).

There are also controversies about whether or not the whole PFC responds similarly to exercise, or if it should be divided into subdivisions. Some global theories describing the PFC, and the changes occurring there as one unit, have been formulated (e.g. RAH-theory), but literature suggests that inhibition is mainly controlled in the RIPFC (20), and working memory is mainly controlled in the DLPFC (6), which means that different tasks might activate different regions of the PFC. Davranche et al (26) found that effect of exercise on the PFC seems to be specific, and cannot be generalized across different cognitive functions, even if they involve similar specific regions of the brain. In the current study, the medial PFC and the DLPFC changes differently than the RIPFC, with significantly higher values of O_2Hb in both HI and LI exercise and in both periods. These findings questions the global aspect of the RAH theory, and supports the idea that the PFC cannot be regarded as one region with a specific reaction to exercise; there seems to be different processes taking place in separate regions within the PFC.

Future research may attempt to clarify these issues by having a more extensive NIRS system on the PFC as well as on the MC, and perhaps also the pre-MC in order to have a more informed image of the global changes in the COX during exercise. Results from different studies also suggest a separation between prolonged exhausting exercise (> 20 min) and shorter maximal exercise (<20 min).

4.3 Cerebral oxygenation of the prefrontal cortex and cognitive performance

Some show cognition to be robust (27) and others show an impairment of cognitive control during exercise (3, 28). The most striking declines in cognitive performance during exercise were reported in a working memory task, a cognitive flexibility and planning task (3, 28, 29). Several studies, including the current one, have shown an increased performance on RT tasks (24, 27). This supports the statement from Davranche, Brisswalter and Radel (27) that exercise induced impairments can be restricted to specific executive functions (like reasoning, working memory, cognitive flexibility), and may not be generalized to cognitive control more broadly. Thus, there seems to be a need for separating between different prefrontal-dependent cognitive tasks when talking about cognitive responses to exercise.

Selective response inhibition is mainly located in the RIPFC (20), and has shown to be robust, and even become more efficient during exercise (24, 27). Thus, in contrast to the inverted-U model (30) and the RAH model, during very hard exercise, selective inhibition control seems to be more efficient towards the end than during the start of exercise. These findings are also supported by the results from the current study, where in the EF task, a faster RT was coupled with a maintained accuracy from initial to ending period in the HI exercise. Interestingly, no difference in performance throughout the LI exercise was observed for the EF task, despite a significantly higher O_2Hb value than in HI exercise. This suggests that cognitive control is maintained at the same level during low intensity exercise, while during higher intensity exercise, the EF task is perhaps more controlled through the implicit system, and therefore become more efficient. Based on earlier studies, a more expected result would be a faster RT towards end, but with more errors (24). As the accuracy of the task was maintained while the RT was faster, this suggests cooperation between the explicit and implicit system. According to dual route models of information processing, this can be due to a conflict between an automatic and rapid response impulse, and a slower, more deliberately controlled response (31). These findings also points toward there being a similar facilitation of cognitive performance on the EF task in prolonged HI exercise, as in shorter maximal exercise (24). The finding that both the selective inhibition control and the oxygenation of the PFC is efficient right before exhaustion state occurs, suggests that it is neither a down-regulation or a deoxygenation of the PFC that is the main limiting factor for prolonged exercise. This is also supported by a study by Jung et al. (25) where they found that a deoxygenation did not seem to be limiting maximum exercise capacity in an incremental cycling exercise until exhaustion.

Performance on the n-back task did not vary between the HI and LI exercise or between the two periods, and does not seem to be similarly affected by intensity of exercise, as the EF task. This leads to some contradicting findings in the current study; although there was an increased O_2Hb value in the DLPFC, no change in performance on the n-back task was observed. Also, no significant increase in O_2Hb values in the RIPFC occurred, but there was an increased performance on the EF task. Thus, the dynamical pattern of selective response inhibition efficiency, differed from the pattern of O_2Hb in the region facilitating this function, as also shown in the study by Schmit et al. (24). This was also the case for the pattern for working memory performance, which remained unchanged throughout both HI and LI exercise, despite a significant increase in O_2Hb. Therefore, the link between the COX of the PFC and the performance on prefrontal dependent cognitive tasks is uncertain. This points to a possible need for more extensive recording of the COX of the MC, the pre-MC and the PFC, in order to have a more informed image of the complex interaction between the different regions, and between the implicit and explicit system during exercise.

4.4 Other possible implications for the relation between the COX and cognition

Fitness level does not only affect the COX, but also cognitive performance; Chang et al. (32) found that fitness level affect cognitive responses during exercise, and Labelle et al. (33) found that low fitness leads to a more unstable cognitive performance. Huttermann and Memmert (30) reported that non-athletes increased cognitive performance up to a certain level, then decreased right before end, which is similar to the pattern described for the COX of the PFC in several studies using shorter maximal exercise (< 20 min). Athletes maintained cognitive performance. Thus, fitness level seems to have an impact both on the COX and on cognitive performance, although the interaction between the COX and cognition is still uncertain.

Another possible implication for the findings in this study could be that an untrained individual who are not experienced with cycling and especially not at the “BrainBike”, could possibly experience a greater oxygenation of the PFC initially because the movement pattern is not familiar enough, and therefore are facilitated partly through the explicit system. The RAH theory predicts a continuous decrease in oxygenation throughout prolonged exercise, and proposes the novel feeling of the NIRS system on the participants head, as an explanation for the initial increase in oxygenation during exercise.

There are many possible implications for the variance in findings, and this underlines the need for more research on the effects of the dynamics of COX and cognition during prolonged aerobic exercise until exhaustion (>20 min).

4.5 Challenges

In the current group there was a large variety among participants, but mostly consisted of untrained individuals. In order to have a continuous variable of fitness (with a power of .80), there should have been twenty-four subjects, but only eleven were included in the study.

In this study, many of the participants reported stopping the exercise because of muscle pain in quadriceps and gluteus, which may have affected the decision to stop before they reached systemic fatigue. If a person is not used to prolonged exercise at a high intensity and is not familiar with pushing own limits, it might be hard for them to push themselves during a HI exercise, and they may quit too early. Therefore, maybe they did not maintain exercise for long enough to experience the shift of the COX before exhaustion, and therefore only the increase of the COX was observed, which is the 2nd step in the three phases proposed by Timikul et al. (12). For further research, it would perhaps be easier to predict the intensity and duration of exercise with a more homogenous group of aerobically trained cyclists who are used to exercising over a prolonged period of time on a high intensity. This would likely also make it easier to match the duration of the control to the duration of exercise, considering the two conditions have to be counterbalanced. It could also reduce the chance of experiencing a novel feeling from the bike, and thereby reduce the possible activation of the PFC. With one or two familiarization sessions with the same protocol as in the experimental sessions, the possibility of experiencing the novel feeling from the NIRS system on the participant's head could also be reduced. In order to have the same duration of exercise in both conditions, a warm up session could have been conducted in the LI exercise also.

The oxygenation during the two cognitive tasks showed no significant difference from each other, suggesting that they either activated similarly in the different regions, or that they did not activate sufficiently in order for the NIRS system to detect the change between them. It could also mean that the NIRS system is not sensitive enough to observe small differences in oxygenation occurring rapidly between nearby regions within the PFC, and further research should be conducted using several prefrontal-dependent cognitive tasks in order to find out more.

4.6 Conclusion

The findings in this study points to the need of separating between different regions within the brain, like the PFC and the MC, as well as within the PFC, when talking about the cerebral limitations to exercise.

The relation between the COX of the PFC and cognitive performance on prefrontal dependent tasks remains uncertain. A faster RT in the EF task was coupled with a maintained accuracy, from initial to ending period in the HI exercise. Interestingly, no difference in performance throughout the LI exercise was observed for the EF task, despite a significantly higher O_2Hb value than in HI exercise. Thus, this study showed that the dynamical pattern for performance on prefrontal dependent cognitive tasks differed from the pattern of O_2Hb in the regions within the PFC, and therefore the link between the COX of the PFC and cognition is uncertain.

The findings in this study do not support the notion that deoxygenation of the prefrontal cortex is involved in the limitation of performance in prolonged (>20 minutes) exercise, as both oxygenation and selective inhibition control remained efficient. Different factors like duration and intensity of exercise, and aerobic fitness level of participants seem to affect both the COX of the brain, and more locally within the PFC, in addition to affecting the complex relation between COX of the PFC and performance on prefrontal dependent cognitive tasks.

This points to a need for more extensive recording of the COX of the MC, the pre-MC and the PFC, in order to have a more informed image of the complex interaction between the different regions, and between the implicit and explicit system during prolonged HI exercise.

5. References

1. Amann M. Pulmonary system limitations to endurance exercise performance in humans. Exp Physiol. 2012;97(3):311-8.
2. Dietrich A, Audiffren M. The reticular-activating hypofrontality (RAH) model of acute exercise. Neuroscience and biobehavioral reviews. 2011;35:1305–25.
3. Dietrich A, Sparling PB. Endurance exercise selectively impairs prefrontal-dependent cognition. Brain and cognition. 2004;55:516–24.
4. Krawczyk DC. Contributions of the prefrontal cortex to the neural basis of human decision making. Neuroscience and biobehavioral reviews. 2002;26(6):631-64.
5. Tandon PN. Not so "silent": The human prefrontal cortex. Neurol India. 2013;61(6):578-80.
6. Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. Hum Brain Mapp. 2005;25(1):46-59.
7. Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. Trends Cogn Sci. 2004;8(4):170-7.
8. Perrey Sp. Non-invasive NIR spectroscopy of human brain function during exercise. Methods. 2008;45:289–99.
9. Cuia X, Braya S, Bryanta DM, Gloverc GH, Reissa AL. A quantitative comparison of NIRS and fMRI across multiple cognitive tasks. NeuroImage. 2011;54:2808-21.
10. Yanagisawa H, Dan I, Tsuzuki D, Kato M, Okamoto M, Kyutoku Y, et al. Acute moderate exercise elicits increased dorsolateral prefrontal activation and improves cognitive performance with Stroop test. NeuroImage. 2010;50:1702-10.
11. Rupp T, Jubeau M, Millet GY, Wuyam B, Levy P, Verges S, et al. Muscle, Prefrontal, and Motor Cortex Oxygenation Profiles During Prolonged Fatiguing Exercise. Advances in Experimental Medicine and Biology. 2013;789(4h prefrontal nirs):149-55.

12. Timinkul A, Kato M, Omori T, Deocaris CC, Ito A, Kizuka T, et al. Enhancing effect of cerebral blood volume by mild exercise in healthy young men: A near-infrared spectroscopy study. Neuroscience Research. 2008;61:242-8.

13. Bhambhani Y, Malik R, Mookerjee S. Cerebral oxygenation declines at exercise intensities above the respiratory compensation threshold. Respiratory Physiology & Neurobiology. 2007;156:196-202.

14. Subudhi AW, Miramon BR, Granger ME, Roach RC, Physiol JA. Frontal and motor cortex oxygenation during maximal exercise in normoxia and hypoxia. J Appl Physiol. 2009;106:1153-8.

15. Rooks CR, Thom NJ, McCully KK, Dishman RK. Effects of incremental exercise on cerebral oxygenation measured by near-infrared spectroscopy: A systematic review. Progress in Neurobiology. 2010;92(134-150).

16. Santos-Concejero J, Billaut F, Grobler L, Oliván J, Noakes TD, Tucker R. Maintained cerebral oxygenation during maximal self-paced exercise in elite Kenyan runners2014 2014-11-20 12:36:21.

17. Suzuki M, Miyai I, Ono T, Odac I, Konishic I, Kochiyamad T, et al. Prefrontal and premotor cortices are involved in adapting walking and running speed on the treadmill: an optical imaging study. NeuroImage. 2004;23(3):1020-6.

18. Nieman DC, Lasasso H, Austin MD, Pearce S, McInnis T, Unick J. Validation of Cosmed's FitMate in measuring exercise metabolism. Research in sports medicine (Print). 2007;15(1):67-75.

19. Borg G. Borg's perceived exertion and pain scales. Champaign, IL, US: Human Kinetics; 1998. viii, 104 p.

20. Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex: one decade on. Trends in cognitive sciences. 2014;18(4):177–85.

21. Haatveit BC, Sundet K, Hugdahl K, Ueland T, Melle I, Andreassen OA. The validity of d prime as a working memory index: results from the "Bergen n-back task". Journal of clinical and experimental neuropsychology. 2010;32(8):871-80.

22. Jurcak V, Tsuzuki D, Dan I. 10/20, 10/10, and 10/5 systems revisited: Their validity as relative head-surface-based positioning systems. NeuroImage. 2007;34(4):1600-11.

23. Abbiss CR, Laursen PB. Models to explain fatigue during prolonged endurance cycling. Sports medicine (Auckland, NZ). 2005;35(10):865-98.

24. Schmit C, Davranche K, Easthope CS, Colson SS, Brisswalter J, Radel Rm. Pushing to the limits: The dynamics of cognitive control during exhausting exercise. Neuropsychologia. 2015.
25. Jung R, Moser M, Baucsek S, Dern S, Schneider S. Activation patterns of different brain areas during incremental exercise measured by near-infrared spectroscopy. Experimental brain research. 2015;233(4):1175-80.
26. Davranche K, McMorris T. Specific effects of acute moderate exercise on cognitive control. Brain and cognition. 2009;69(3):565-70.
27. Davranche K, Brisswalter J, Radel R. Where are the limits of the effects of exercise intensity on cognitive control? Journal of Sport and Health Science. 2015;4(1):56-63.
28. Del Giorno JM, Hall EE, O'Leary KC, Bixby WR, Miller PC. Cognitive function during acute exercise: a test of the transient hypofrontality theory. Journal of sport & exercise psychology. 2010;32(3):312-23.
29. Paas FG, Adam JJ. Human information processing during physical exercise. Ergonomics. 1991;34(11):1385-97.
30. Hüttermann S, Memmert D. Does the inverted-U function disappear in expert athletes? An analysis of the attentional behavior under physical exercise of athletes and non-athletes. Physiology & Behavior. 2014;131(0):87-92.
31. De Jong R, Liang CC, Lauber E. Conditional and unconditional automaticity: a dual-process model of effects of spatial stimulus-response correspondence. Journal of experimental psychology Human perception and performance. 1994;20(4):731-50.
32. Chang YK, Labban JD, Gapin JI, Etnier JL. The effects of acute exercise on cognitive performance: A meta-analysis. Brain Research. 2012;1453(0):87-101.
33. Labelle V, Bosquet L, Mekary S, Bherer L. Decline in executive control during acute bouts of exercise as a function of exercise intensity and fitness level. Brain and cognition. 2013;81(1):10-7.