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INVESTIGATION OF AN EXERCISE-INDUCED STATE OF HYPOFRONTALITY

AND ITS POTENTIAL ASSOCIATION WITH CENTRAL FATIGUE

Master Thesis

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Abstract

The reticular-activating hypofrontality model of acute exercise (RAH) predicts exercise-induced hypoactivity in frontal cortex which mediates executive function. Connors Continuous Performance Test (CCPT) was used to investigate changes in executive function during- and post treadmill running in healthy volunteers (n=30, 15 male). In a randomized order, subjects performed the CCPT at rest, during low- (LI; 63% maximal heart rate; MHR) and moderate intensity (MI; 75% MHR). Separately, subjects then performed isocalorifically matched exercise bouts of LI, MI and high intensity interval training (HIT) consisting of 4x4 min with 90% MHR and 3 min recovery at 60-70% MHR. Repeated measures ANOVAs revealed main effects of exercise intensity for reaction time RT during- ($p \leq 0.001$) and post exercise ($p \leq 0.0001$). Subsequent analyses showed an overall increase of RT during exercise compared to rest ($p \leq 0.005$). RT decreased significantly from rest to post exercise levels in an exercise intensity dependent, linear fashion ($p \leq 0.0001$). Commission errors showed a non significant linear trend to increase both during ($p=0.057$), and post exercise ($p=0.052$) as a function of intensity. In a follow up study, we sought to relate observed exercise effects to frontal cortex activity through the use of transcranial direct current stimulation (tDCS) (n=4) and transcranial magnetic stimulation (TMS) over the dorsolateral prefrontal cortex (DLPFC). Prior to TMS stimulation cortical excitability was estimated post running through motor-evoked potentials (MEP) elicited from the primary motor cortex (M1) induced by single burst TMS and measured in the first dorsal interosseous (FDI) muscle using electromyography. At rest, inhibitory cathodal tDCS with left DLPFC cathode and right supraorbital anode led to improved reaction time and increased amount of commission errors, whereas anodal stimulatory tDCS in the immediate post exercise period was unable to recover the post exercise effect. Continuous theta burst stimulation over the left DLPFC post running further impaired inhibitory control and facilitated reaction time. Different findings during- and after- exercise suggests that potential contributing mechanisms such as computational and metabolic factors may be differentially active during these respective conditions. Furthermore, the fact that an inhibitory TMS protocol pronounced the post running effects even more and that we were able to mimic the reported RAH effects at rest with inhibitory frontal tDCS, but observed different patterns during exercise, suggests that the latter state cannot be fully explained by reducing activity in the left frontal cortex alone. Failure to modify the after exercise effect with stimulatory tDCS also supports an interplay of different factors and might emphasize the strong, robust effects of exercise that cannot simply be attenuated by current application. Increases in MEP post running for 35min paired with the observed performance decrements imply an excited state of M1 and might serve as an explanatory cross-link to central fatigue suggesting that a hypofrontal state might enhance the motor cortical drive to activate muscles.

Acknowledgement

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Abbreviations

^{18}FDG	18-fluorodeoxyglucose
5-HT	5-hydroxy-tryptamine
AADC	Aromatic ʟ-amino acid decarboxylase
ACC	Anterior cingulate cortex
ACSM	American College of Sport Medicine
ACTH	Andrenocorticotropin hormone
ADHD	Attention deficit hyperactivity disorder
ANOVA	Analysis of variance
ANS	Autonomic nervous system
BBEP	Biomedical Basis of Elite Performance
BDNF	Brain-derived neurotrophic factor
BOLD	Blood-oxygen-level-dependent
BW	Body weight
cAMP	Cyclic adenosinemonophsophate
CBF	Cerebral blood flow
CCPT	Conners Continuous Performance Test
CFF	Critical flicker fusion
CMR_{CHO}	Cerebral metabolic rates of carbohydrate
CMR_{O2}	Cerebral metabolic rates of oxygen
CNS	Central Nervous System
CP-316,819	Glycogen phosphorylase inhibitor
CPT	Continuous Performance Test
CRH	Corticotropin releasing hormone
cTBS	Continuous theta burst stimulation
D1	Dopamine receptor 1
D2	Dopamine receptor 2
DLPFC	Dorsolateral prefrontal cortex
DOPAC	3,4-dihydroxyphenylacetic acid
EEG	Electroencephalography
EMG	Electromyography
ERN	Error-related negativity
FDI	First dorsal interosseous
fMRI	Functional magnetic resonance imaging
fNIRS	Functional near-infrared-spectroscopy
HI	High intensity

IV

HPA	Hypothalamic-pituitary-adrenal
HR_{max}	Maximal heart rate
HVA	Homovanillic acid
IFC	Inferior frontal cortex
ISI	Interstimuli interval
LCGU	Local cerebral glucose utilization
LGN	Lateral geniculate nucleus
LI	Low intensity
M1	Primary motor cortex
MEP	Motor-evoked potential
MHPG	3-methoxy 4-hydrosypheylglycol
MI	Moderate intensity
MS	Multiple sclerosis
MVC	Maximal voluntary contraction
NA	Negative Affection
OCD	Obsessive compulsive disorder
oxyHB	Oxygenated hemoglobin
PA	Positive Affection
PANAS	Positive affection negative affection score
PFC	Prefrontal Cortex
POMC	Preproopiomelancortin
PVN	Paraventricular neurons
R	Respiratory exchange ratio
RAH	Reticular-activating hypofrontality
rCBF	Regional cerebral blood flow
RPE	Rate of perceived exertion
RT	Reaction time
SAS	Sympathoadrenal system
SD	Standard deviation
SfN	Society for Neuroscience
SMA	Supplementary motor area
SPECT	single photon emission computed tomography
STN	Subthalamic nucleus
T_A	Threshold for adrenaline release
TBI	Traumatic brain injury
tDCS	Transcranial direct current stimulation
TEE	Total amount of energy expended

TMS	Transcranial magnetic stimulation
T_{NA}	Threshold for noradrenaline release
TOP	Temporal, occipital parietal
UCL	University College London
VMPFC	Ventromedial prefrontal cortex
VO_{2max}	Maximal aerobic capacity
VT	Ventilatory Threshold
WCST	Wisconsin Card Sorting Test
W_{MAX}	Maximal power output
ι-DOPA	3, 4 dihydroxy-ι-phenylalanine
χ^2	Chi-square

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1   Introduction

It is well accepted from experimental and anecdotal evidence that exercise alters the mental state and cognitive function. Moderate aerobic exercise has been shown to promote emotional wellbeing by alleviating stress, decreasing anxiety and lower depression (Salmon 2001). Even though several authors repeat an antidepressant and anxiolytic effect of voluntary exercise also in rodents (Brene et al. 2007; Duman et al. 2008; Greenwood et al. 2003) such a finding is not consistent (Dubreucq et al. 2010; Fuss et al. 2010). Exercise is also beneficial to cognition and mood (Colcombe & Kramer 2003; Tomporowski 2003) and furthermore implies long-term mood improvements (Steptoe and Butler 1996). Several models have attempted to explain these effects. The reticular-activating hypofrontality model combines the activating neuromodulatory approach with a suggested, superimposed decrease of frontal cortex activity during an acute bout of exercise. There is a wide range of studies pointing towards such an event, however, there is also conflicting literature concerning effects on mood and particular cognitive functions for which the prefrontal cortex with its executive system has been identified. Moreover, other explanatory suggestions involving endorphins and endocannabinoid seem to complicate the matter. The present study therefore attempted to investigate effects of different exercise intensity during and post treadmill running on executive system using the Conners Continuous Performance test. In a second part, the state of hypofrontality was attempted to be simulated using transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS).

1.1   Reticular-Activating System

The first notion of a neuroendocrinological explanation for a link between exercise and cognition was stated by Cooper (1973) and later taken up by Chmura et al. (1994). Noradrenaline, adrenaline, 5-hydroxy-tryptamine (5-HT) and dopamine are held in vesicles once synthesized and act as neurotransmitters by innervating different pathways.

Catecholamine-synthesis happens in chromaffin cells and starts with hydrogenation of phenylalanine, which is converted to tyrosine with phenylalanine hydroxylase as a catalyst for the reaction. Tyrosine is broken down into metabolite 3, 4 dihydroxy-ι-phenylalanine (ι-DOPA) under the influence of tyrosine hydroxylase, located in all catecholamine-synthesizing cells. When ι-DOPA is catalysed by DOPA decarboxylase dopamine forms, which can synthesize noradrenaline in the presence of dopamine-β-hydroxylase. Both are mainly stored in vesicles. The noradrenaline that gets to the adrenal medulla can get N-methylated into adrenaline, which is then transported, back into chromaffin granules for storage (Kuhar et al. 1999).
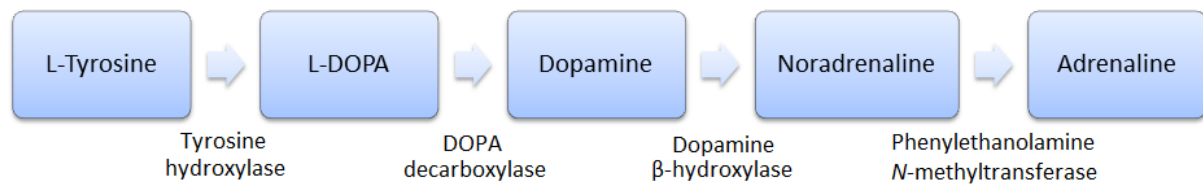
Figure 1: Catecholamine synthesis
Note. Catecholamine synthesis consists of several steps starting with L-tyrosine that converts to L-DOPA under influence of tyrosine hydroxylase. L-DOPA is the precursor for dopamine when the enzyme DOPA decarboxylase is present. Dopamine can further trigger noradrenaline synthesis with dopamine β-hydroxylase. Adrenaline is formed from noradrenaline under the influence of phenylethanolamine *N*-methyltransferase, adapted from McMorris (2009).

Noradrenaline-containing neurons are mainly located in the locus coeruleus from where they project throughout the entire cerebral cortex and cerebellum. Dopamine cell bodies are mainly located in the substantia nigra and ventral tegmental areas and their axons innervate primarily the corpus striatum. 5-HT containing neurons are mostly found in the raphe nucleus and their projections involve nearly the entire brain.

Strong representations are found in the pons, midbrain, amygdala, hippocampus, hypothalamus and thalamus while intermediate density involves the cerebellum and cerebral cortex (Kuhar et al. 1999). However, once released from the vesicles, the effect of these neurotransmitter substances depends on the postsynaptic receptors. Noradrenaline taken up by β-receptors stimulates adenyl cyclase, leading to synthesis of a second messenger, cyclic adenosinemonophsophate (cAMP), which amplifies the effect of neuronal activity whereas an activated α-receptor inhibits adenyl cyclase activity, which leads to a controlling effect on transmitter release due to the negative feedback of the not activated second messenger (Arnsten 1997). Similarly there are dopamine receptors that stimulate (D1 receptors) and those that inhibit (D2 receptors) adenyl cyclase activity. The 5-HT1 receptor inhibits in a similar manner to α-adrenergic and D-type receptors whereas their stimulatory counterparts are not linked to adenyl cyclase activity (Alex & Pehek 2007).

During and even immediately before, exercise the sympathoadrenal system (SAS), as part of the autonomic nervous system (ANS) gets activated by the hypothalamus and brainstem resulting in selective postganglionic release of catecholamines. With increasing exercise intensity adrenaline and to a lesser extend, noradrenaline get released from the adrenal medulla to ensure glycolysis and lipolysis for efficient utilization of glycogen and fat metabolism, respectively.
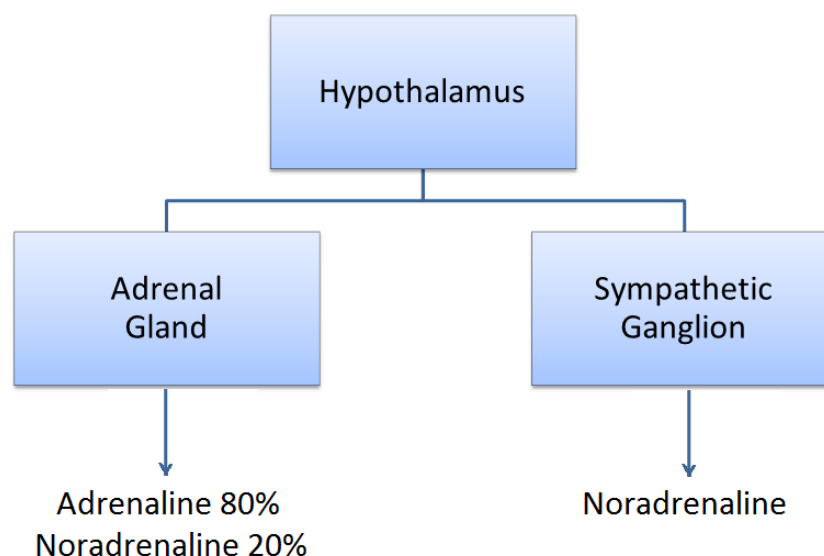
Figure 2: Sympathoadrenal system
Note. The sympathoadrenal system is depicted and indicates that the hypothalamus is involved in adrenaline and to a lesser extend noradrenaline release from the adrenal gland as well as noradrenaline release from the sympathetic ganglion, adapted from McMorris (2009).

It has been suggested that catecholamine release in the periphery has an interactional trigger for its release in the brain and vice versa (Genuth 2004). Without doubt a crucial role in this process plays ANS feedback through the thalamus, reticular activation system and limbic system to the hypothalamus reflecting pain, glycogen depletion and cardiorespiratory stress. The hypothalamus response then releases catecholamines peripherally and possibly centrally (Genuth 2004) as well as stimulates the hypothalamic-pituitary-adrenal (HPA) axis. HPA activity results in corticotropin releasing hormone (CRH), which is after synthesizing in the paraventricular neurons (PVN) in the hypothalamus secreted into hypophyseal vessels in the median eminence where the precursor preproopiomelancortin (POMC) serves to form andrenocorticotropin hormone (ACTH) secreted by anterior pituitary corticotrophs. After diffusing into the zona fasciculate of the adrenal cortex, ACTH leads to synthesis and secretion of the hormone cortisol (Genuth 2004). Argenine vasopressin (AVP), another secretagogue of cortisol plays an important role in synthesis of cortisol in a dehydrated state. Cortisol has various effects during exercise. First, it produces glucose from proteins (catabolic effect), facilitates fat oxidation and maintains blood pressure. Second, cortisol not only blocks hypothalamic release, leading to regulation of CRH concentration but also inhibits transcription of POMC into ACTH in the pituitary. The latter effect disappears in prolonged and/or strenuous exercise bouts. Instead, AVP is oversecreted into the pituitary circulation causing accumulation of ACTH, which cannot be balanced by cortisol (Deuster et al. 1989). Moreover, noradrenaline triggers increases in CRH synthesis, which in turn increases adrenaline synthesis and release resulting in ACTH synthesis in the pituitary.

When tryptophan is transported from the blood to the brain 5-hydroxytryptophan is built in the raphe nuclei under the influence of tryptophan hydroxylase.
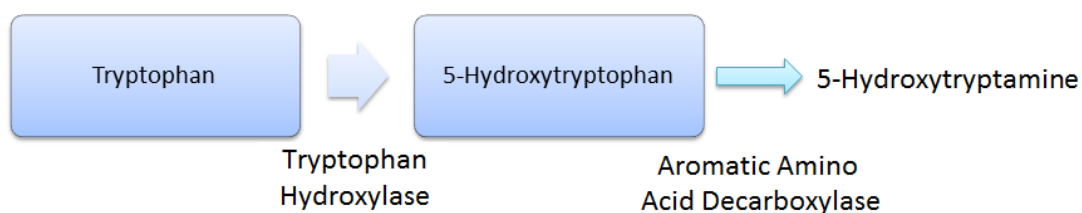
Figure 3: 5-HT synthesis
Note. The synthesis of 5-Hydroxytryptamine starts with tryptophan, which can readily cross the blood-brain barrier when unbound from fatty acids. Tryptophan hydroxylase catalyses the reaction converting tryptophan to 5-Hydroxytryptamine, adapted from McMorris (2009)

This compound forms into 5-HT when it is broken down by aromatic ι-amino acid decarboxylase (AADC). Tryptophan, the precursor of 5-HT is located in plasma either bound to albumin or in an unbound form, which can readily cross the blood brain barrier. Acute exercise results in an increase in unbound tryptophan because free fatty acids displace tryptophan from binding with albumin (Chaouloff et al. 1986). AADC is also the link to dopamine synthesis by converting DOPA into dopamine. Interestingly, blood pH amongst other various substrates distinguishes the destiny of AADC (dopamine or 5-HT) (Frazer & Hensler 1999). Furthermore, 5-HT triggers ACTH synthesis and secretion from the pituitary, CRH in the hypothalamus and cortisol in the adrenal cortex (Alex & Pehek 2007).
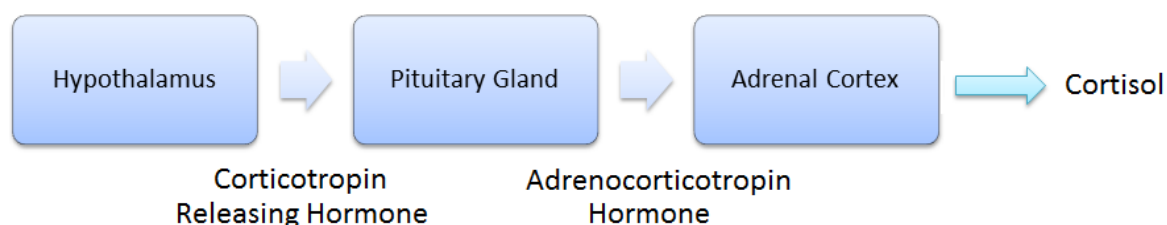
Figure 4: HPA axis
Note. The main steps in cortisol production in the hypothalamic-pituitary-adrenal axis. Upon stimulation the hypothalamus releases corticotropin releasing hormone, which stimulates the pituitary gland. There, adrenocorticotropin hormone acts on the adrenal cortex, resulting in cortisol release, adapted from McMorris (2009).

Since only a very small amount of catecholamines were shown to be able to cross the blood brain barrier (Cornford et al. 1982), whose endothelial cells have tight junctions preventing transcapillary movement of molecules, and peripheral plasma concentrations would have to be unrealistically high to cross this barrier as indicated by rat models (McGaugh 1983) different methods are needed to assess changes in brain neurotransmitters or animal models can help. Animals studies show increased dopamine concentrations during and after acute exercise in the brainstem and hypothalamus (Meeusen et al. 2001) when intensity passes a threshold level (Hattori et al. 1994) and in response to chronic exercise in hypothalamus and midbrain but decreases in the prefrontal cortex, hippocampus and striatum (Meeusen et al. 1996). However, whole brain noradrenaline concentrations in animals either showed a decrease or no significant effect with regional variations (McMorris et al. 1999). In

particular, the brainstem, hippocampus, pons medulla, midbrain and hypothalamus showed decreases and the striatum increases whereas chronic exercise, which resulted in lower whole brain concentrations, led to increases in the hypothalamus (Meeusen et al. 2001). The literature for catecholamines, however, seems more agreeing on an increased turnover rate during exercise and increased catecholamine metabolites have also been found after acute exercise. While increased concentrations of the noradrenaline metabolite 3-methoxy 4-hydrosypheylglycol (MHPG) was found in most brain regions, increased amounts of the dopamine metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and 4-hydroxy 3-methoxyphenylacetic acid or homovanillic acid (HVA) were suggested in the brainstem and hypothalamus (Meeusen et al. 1997). Plasma concentration of MHPG was furthermore shown to be closely related to its concentration in the CSF (Stuerenburg & Kunze 1998) and central and plasma HVA concentrations were also close.

In contrast to the catecholamines 5-HT is not affected by the blood brain barrier but instead exercise increases unbound tryptophan, which can cross the blood brain barrier. Animal studies show time-dependent increases in whole brain 5-HT concentrations, particularly in the brainstem, hippocampus and hypothalamus (Meeusen et al. 2001), which are likely due to individual time course to use fat as the main energy supply to unbind tryptophan from its fatty acid attachment. This notion would suggest low, long enduring exercise bouts to elevate 5-HT in the brain.

To associate neurotransmitters with exercise and cognition calculations of adrenaline (T_A) and noradrenaline (T_{NA}) thresholds have been suggested in human studies because their plasma concentration rises exponentially (Green et al. 1983) when exercise reaches an intensity threshold (see figure 5), which was shown to be at or above 75% VO_{2max} (Podolin et al. 1991) but T_A levels can vary from 40% W_{MAX} to 80% W_{MAX}, with fitter individuals holding higher thresholds (McMorris 2009). At this point catecholamines are secreted into the blood via the adrenal medulla and postganglionic cells. Significant improvements in speed of decisions during a soccer-specific, decision-making test were observed at T_A and maintained during W_{MAX} (McMorris et al. 1999). However, such an improvement was not found following exercise at T_A or W_{MAX} in a soccer-specific psychomotor task (McMorris et al. 2000), which is likely due to either the short half-life of adrenaline making an estimation of arousal difficult post exercise or the simplicity of the cognitive variable. Therefore, in a further study McMorris et al. (2003) investigated reaction time and movement time in a noncompatible choice-response-time task at 70% and 100% W_{MAX}, which included four lights and four buttons that were supposed to be connected differently as soon as one of the lights flashed up (light one with button three, light two with button four, light three with button one, and light four with button two) hence involving short-term memory. Neither adrenaline nor noradrenaline were significantly correlated with performance and the only significant results was a decrease in movement time at 100% W_{MAX}. A more recent study of McMorris et al. (2008b) examined performance of the flanker task (Eriksen & Eriksen

1974) during exercise at 50% and 80% W_{MAX} and simultaneously looked at plasma concentrations of adrenaline, noradrenaline, cortisol and ACTH. Even though both, post-exercise adrenaline and noradrenaline concentrations showed a linear increase from rest to 80% W_{MAX} only adrenaline had a large pre/post rise at both, 50% and 80% W_{MAX} conditions whereas for noradrenaline this rise was only observable between rest and 80% W_{MAX}. Pre-exercise levels of these catecholamines were also higher than baseline. Interestingly, for the cognitive measures an inverted-U effect was observed for reaction time and a linear decrease for errors in performance (inhibition of response to noise letter), which was correlated with the change in noradrenaline suggesting a relationship between increases in arousal and increased inhibition error. In contrast to the catecholamines the HPA hormones changed differently. While cortisol changed little, ACTH demonstrated a large increase after the 80% W_{MAX} exercise condition, pointing towards a slower diffusion rate for cortisol (Deuster et al. 1989). Thus, the measured plasma concentrations of these two hormones do not mirror brain concentrations at thee same time and it should be taken into consideration that cortisol can inhibit ACTH synthesis and CRH release. However, when too much stress is present cortisol is unable to control those two arousal substances, possibly leading to over-arousal as seen in inverted U findings. Moreover, the change in adrenaline combined with the change in ACTH correlated with the changes in reaction time but not accuracy in a way that smaller increases in those two predictors would lead to greater increases in reaction time. McMorris et al. (2008b) attribute this observation to the assumption that the flanker task involved the PFC, which was suggested to be susceptible to increases in stress (Jahanshahi & Dirnberger 1999; Vedhara et al. 2000). Furthermore, previous research indicates decreased motor time in when adrenaline and ACTH have a large increase (Davranche et al. 2005), which in the study of McMorris et al. (2008b) was associated with large increases in processing time. Consequently, slowing in central processing time involving PFC might be off-set by faster motor times giving a smaller increase in reaction time in response to large increases in neurotransmitters.
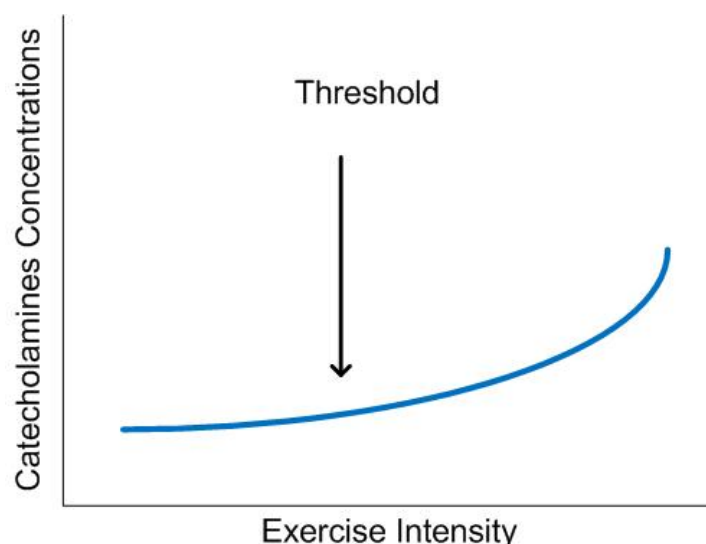
Figure 5: Threshold for Catecholamine release
Note. On the x-axis intensity of exercise is depicted. Y-axis shows catecholamine concentration. The Threshold for catecholamine levels to rise is indicated with an arrow but can vary between 40% and 80% W_{MAX} depending on catecholamine, adapted from McMorris 2009.

Aerobic exercise (< 2mmol l-1) and anaerobic exercise (> 10mmol l-1) led to similar quadratic effect for accuracy of learning in a vocabulary learning task post exercise but only anaerobic repeated sprints led to both, faster learning time, which was also correlated with measured dopamine concentrations, and increases in adrenaline and noradrenaline concentrations (Winter et al. 2007). Splitting up participants to exercise 10% above and below (75% workload eliciting lactic threshold; TLA) TLA for 20min and 60min, respectively led to linearly decreased choice reaction time in the 75% TLA group up to 40min and also to improvements in the above TLA group after 10min, which was correlated to plasma concentrations of adrenaline and noradrenaline for the above TLA group only.

Similarly, Grego et al. (2004) investigated catecholamine changes in long duration (180min) cycling at 66% VO_{2max} but incorporated examination of HPA activity and EEG measures. The auditory oddball task used in that study required a distinction between an auditory target and a distractor. In general they found increases in the P300 amplitude and P300 latency towards the end of exercising, pointing towards changes in amount and speed of processing, respectively. However, the exercise condition was unfortunately not compared to the control condition. Adrenaline and cortisol was shown to increase after the 108th minute, which was not correlated with EEG changes and noradrenaline got not affected.

To see if cognitive performance affects plasma MHPG and HVA concentrations, McMorris et al. (2008b) compared the concentration of these metabolites in a exercise only session to a exercise plus cognition condition, which consisted of a random number generation test (Baddeley et al. 1998) – a test of working memory. Test performance, as measured by reaction, movement and total response time during 40% and 80% W_{MAX} was not affected by exercise. However, during 80% W_{MAX} there was

a significant increase in reaction time that was paired with a decrease in movement time. MHPG change was affected by exercise intensity and highest during 80% W_{MAX} with no significant interaction effect. Even though no effects of HVA were observed, combined HVA and MHPG concentrations served as strong predictors of a change in performance of the cognitive test, movement time and total response time.

Reaction time is the time from the onset of the stimulus to the beginning of an overt response. In contrast, visual reaction time can be broken down into reception time, the time for the visual perception to project from the eyes to the primary visual cortex, opto-motor integration time, the time for the perception and localization of the visual stimulus to organize a motor response and motor outflow time, the time from the intention to the initiation of the motor action (McMorris 2009). This has also been described as the information transfer task because the presence of the stimulus only has to be reorganized and then trigger a pre-determined response (Humphreys & Revelle 1984). Such simple reaction tasks have been shown to activate the basal ganglia, lateral premotor cortex, cerebellum and parietal lobe, which also primarily have noradrenaline and dopamine as their main neurotransmitters (Critchley et al. 2003). Therefore, results of catecholamine and reaction time interactions are not surprising (Robbins 2002). According to Baddeley (1986) tasks involving the working memory have three inter-dependent parts:, the phonological loop, encoding acoustic and visual information, the visuospatial sketchpad, processing visual and visuospatial information and central executive mechanisms to control and oversee the whole process. Hence, the phonological loop, involving lateral frontal and interior parietal lobes of the left hemisphere and the visuospatial sketch pad, situated in the parieto-occipital region mainly of the right hemisphere (Barbas 2000) are responsible for retaining verbal and visual information, respectively, in short-term memory. The PFC, which is involved in central executive performance (Critchley et al. 2003; Seamans et al. 2003) also recalls past experience from long-term memory held in post-sensory regions of the temporal and parietal cortices and integrates it with perception of present stimuli. This is evidenced by strong connections of temporal and parietal areas with the PFC (Gazzaniga et al. 2001). Furthermore, the basal ganglia plays a crucial role in short-term memory processes and is connected to the DLPFC in central executive tasks (Frith et al. 1991). Importantly, these areas are all activated by dopaminergic and noradrenergic pathways (Chamberlain et al. 2006).

Summing up studies investigating neurotransmitter changes as a potential explanation for changes in cognitive performance leads to the conclusion that working memory tasks and tasks reaction time, even with its subdivisions, get differently affected by exercise, which might be due to more required activation for working memory tasks or the fact that noradrenaline and dopamine are also the main neurotransmitters for the premotor cortex and supplementary motor areas to control movement. Therefore there might be some sort of limitation when both movement and cognitive tasks are

executed simultaneously. Moreover, stress, as in exercise, activates the limbic system including the amygdala, which either leads to improvements in cognition in response to moderate increases in arousal (Nielson & Powless 2007) or to a negative effect as the amygdala gets further activated (Roozendaal et al. 2006). Another issue are cognitive differences in fit and unfit individuals in response to exercise. Brisswalter et al. (1997) documented a positive effect of exercise in fit and an inverted U effect in unfit individuals even though they were exercising at the same relative intensities. This was suggested to be due to different feedback from the ANS to the CNS given that earlier increases in noradrenaline, adrenaline and lactate are seen in the unfit (Acosta et al. 2001), the later of which is associated with perception of pain.

A study that supports the notion of an involvement of the RAS found improved reaction speeds and an interaction between exercise and the arousing effect of a loud auditory signal in an auditory two-choice reaction time task during 40min of cycling compared to at rest (Audriffen et al. 2008). This suggests a direct link between arousal and activation. Moreover, in the same study reaction time was found to peak between 15-20min and after exercise cessation increased to baseline very quickly. Interestingly, the improvement in reaction time was due to energizing motor outputs. This was found by fractionating reaction time into the components premotor time and motor time. Hence, it would seem unlikely that exercise influences sensory and perceptual processes via arousing systems. Enhanced motor time and not premotor time is in accordance with Sanders information processing model (Sanders 1983). However, interactions between the effect of signal intensity and the effect of exercise on premotor time have also been observed (Davranche et al. 2005; Davranche et al. 2006). Sternberg´s additive factors method (Steinberg 1969) would in addition predict exercise to enhance sensory processes. This could be supported by studies showing exercise-induced increases in the critical flicker fusion frequency threshold (Davranche & Audriffen 2005; Davranche et al. 2005). Taken together, it appears that exercise on the one hand positively modifies peripheral sensory processes involved in early sensory processing mechanisms, and on the other hand increases efficiency in the cortico-spinal command, reflecting improved late motor processes. When comparing intensities, it seems like movement time experiences an effect reflecting an inverted U (Draper, McMorris & Parker 2010). In conclusion, the neuroendocrinological rationale alone for acute effects of exercise on cognition is strong in theory but not very well supported by empirical data.

In summary, immediately before and during exercise the hypothalamus elicits synthesis of SAS and catecholamines. ANS feedback to the hypothalamus triggers further activity by the SAS and releases noradrenaline and dopamine, which are both synthesized in the brain into their respective pathways in the brain affecting cognition. As intensity increases beyond a threshold adrenaline and less noradrenaline are released from the adrenal medulla to the postganglionic cell in the blood. The hypothalamus also triggers cortisol via the HPA, which moderates HPA activity. However, on higher

intensities, the controlling effect of cortisol disappears and CRH and ACTH lead to more arousal, involving the limbic system at the expense of the cognitive brain areas such as the PFC. On higher intensity also Noradrenaline and dopamine rise. The latter activates the limbic system too but its production is block by longer during exercise that involves fat metabolism and therefore leads to a rise in 5-HT by unbinding tryptophan from its fatty acids in the periphery.

Endogenous opioid release has been named to account for psychophysical changes during running or more precisely to explain a state called "runner´s high" which has been described as a state of euphoria during prolonged running. This phenomenon has non-scientifically been described as ''pleasantness,'' ''inner harmony,'' ''boundless energy'' (Boecker et al. 2008) but has mostly exclusively been supported by peripheral opioid measurement. Rat studies, however, showed altered opiate cerebrospinal fluid levels (Hoffmann et al. 1990) as well as receptor occupancy (Tendzegolskis et al. 1991; Aravich et al. 1993) in response to running. In addition, in mice that were exposed to regular swimming naloxone triggered similar withdrawal symptoms as those of chronic morphine treatment (Christie & Chesher 1982). In humans peripheral increases of plasma β -endorphin in the 5-fold range has been evidenced after exercise (Carr et al. 1981; Farrell et al. 1982; Wildmann et al. 1986). A review adds details to this notion by indicating that endorphin alterations depend on the type of exercise and special populations tested, and may be different in individuals with health problems (Goldfarb & Jamurtas 1997). Only recently, β-endorphin (Koehl et al. 2008) and endogenous endocannabinoid signaling (Hill et al. 2010) released during running have been identified as a key factors for exercise-induced cell proliferation in the hippocampus which mediates experience-induced plasticity. However, the notion that endocannabinoid are necessary for such a cell proliferation in the hippocampus has been challenged by Dubreucq et al. (2010) who found increased neurogenesis in the hippocampus in both CB1 knockout and control mice. The only study looking at central opioid changes during exercise investigated ligand activation with the nonspecific opioidergic ligand [18F]FDPN using PET (Boecker et al. 2008). They found central opioid receptor binding (unspecifically mu, kappa, delta opioid receptors) after 2h of strenuous, long-distance running in prefrontal and limbic/paralimbic brain regions, involving prefrontal/orbitofrontal cortices, anterior cingulate cortex (ACC), bilateral insula, parainsular cortex and temporoparietal regions. Particularly the (fronto)limbic areas connected with emotions, mood and affect might play a important role in euphoria experienced during running, which might be associated with a reward system to possibly reinforce the important health benefits of exercising in evolutionary terms. However, neither the nucleus accumbens, a key player in reward and opioid-dopamine interactions, showed opioidergic changes (Boecker et al. 2008) nor did the dopaminergic system as evidenced by no significant increased striatal dopamine release in response to treadmill running for 30min using [11C]raclopride PET (Wang et al. 2000). No neuropsychological tests were applied in both studies making it difficult to estimate if a state of euphoria was achieved. Most importantly, in the presence of naloxone, a opioid

receptor antagonist changes in mood still occur and therefore the least that can be said is that if for a unknown reason there is a sudden elevated release of endorphins centrally as suggested by Boecker et al. (2008), then it is not the only mechanism contributing to changes in mood in response to exercise.

In humans elevated plasma anandamide levels have been observed in response to exercise leading to activation of the endocannabinoid system (Sparling et al. 2003). Thereafter rodent studies have been carried out to investigate the influence of endocannabinoids on voluntary wheel running (Hill et al. 2010; Keeney et al. 2008; Zhou & Shearman 2004). In contrast, pharmacological studies face problems such as system applications, local concentration variations and different central and peripheral functional mechanisms. CB1 knockout in mutagenic mice led to 30-40% less running activity compared to controls (Dubreucq et al. 2010), pointing towards a major link to rewarding mechanisms. Both blockade and CB1 receptor deletion have earlier been shown to attenuate reward-driven behaviours in central reward pathways (Maldonado et al. 2006). Moreover, CB1 knockout mice had impaired hippocampal neurogenesis, which, however had no consequences on the behavioral level assessed by a force swim test and was not impaired but instead increased to the same extent as in the control group in response to exercise (Dubreucq et al. 2010) indicating that running-induced neurogenesis is independent of the endocannabinoid system. This is opposed to the conclusion of Hill et al. (2010) underlying the necessity of the endocannabinoid system for hippocampal neurogenesis. Endocannabinoid signalling does not account for emotional changes observed during running but rather produces controversial results (Burghardt et al. 2004; Duman et al. 2008; Fuss et al. 2010) with some studies reporting moderated anxiety in rodents after running and some indicating an anxiogenic effect, likely due to elevated neurogenesis after running (Fuss & Gass 2010). Also the study of Dubreucq et al. (2010) found no differences in anxiety behaviour after voluntary wheel running in CB1 knockout or control mice despite a concurrent rise in neurogenesis by 40% and the finding of reduced anxiety behaviour during baseline condition in CB1 knockout mice that paralleled with decreased basal neurogenesis rates. In summary, activation of the endocannabinoid system through exercise alone can not sufficiently explain mood effects of exercise as CB1 and CB2 receptors do not appear to be expressed in brain regions corresponding to mood effects, except maybe the amygdala. Rather, exercise-induced anandamide release acts on CB1 receptors in the olfactory bulb and hippocampus, mainly on microglia serving as a reward mechanism and leading to neurogenesis. This might explain chronic changes in mood and emotions in response to exercise. Moreover, in terms of executive function it could be shown that 9-tetra-hydrocannabinol and marijuana acutely increase impulsive responds in a stop-signal task in humans (McDonald et al. 2003; Ramaekers et al. 2006) measuring response inhibition. Marijuana application further impaired choice selection in a task in which two options lead to either monetary gain or loss (Lane & Cherek 2002) and led to more risky behavior (Lane et al. 2005). In rat studies the cannabinoid agonist WIN55,212-2 was found to mildly impair response inhibition but not change decision-making in the stop-signal and delay discounting

task, respectively (Pattij et al. 2007). Conversely, the selective CB1 receptor blocker rimonabant reduced impulsive responding in a visuospatial attention task (Pattij et al. 2007). Interestingly, tonic, endocannabinoid-induced activation of cannabinoid CB1 receptor has been suggested to underestimate time estimation (Han & Robinson 2001), which is presumably modulated within the striatum as a interaction effect of glutamatergic projections from the prefrontal cortex and afferent dopaminergic connections from the substantia nigra (Meck & Benson 2002).

1.2   Explicit VS Implicit Information Processing and the Executive Network

Cognitive function has been influenced by evolutionary pressures to develop more integrative neural structures allowing processing of increasingly complex information with the prefrontal cortex, which provides the neural basis of higher cognitive functions (Fuster 2000a) at the top of this hierarchy. While the emotional system allows to evaluate incoming information, hence connecting it with biological significance in a nonalgorithmic, skilled-based fashion (Churchland 2002) including an emotional memory, the cognitive system processes information in a separate and parallel manner for perceptual evaluation of the environment and involves a perceptual and conceptual memory (LeDoux 1996). These two functional and anatomical distinguished systems already diverge at the level of the thalamus whereby emotional content is processed in the amygdala (LeDoux 1996) whose computational product of affection if further processed in the cingulate cortex and ventromedial prefrontal cortex (VMPFC) (Damasio 1994) representing parts of the limbic system. Amygdala lesions typically impair basic emotions such as happiness or fear whereas VMPFC lesions are associated with more complex impairments of social emotions, for instance. The cognitive system is represented by the hippocampus and temporal, occipital and parietal cortices (TOP), which are all regarded as another set of limbic structures involved in both, perception and long-term memory (Dietrich 2004) and also incorporate primary sensory cortices located in TOP as well as its association cortex that further assimilates sensory information originally decoded in the primary cortex. Furthermore, these structures provide selective attention (Taylor 2001). Although there is cross-talk between the emotional and cognitive system at lower levels, reintegration of their computational products happens on the level of the dorsal lateral prefrontal cortex (DLPFC) (Fuster 2000b), which, however, does neither directly receive sensory information nor is able to store long-term memory or is part of emotional computation. Due to specific properties of the DLPFC such as executive function, which has been suggested as the ability to further integrate already highly processed and computed information to allow even higher cognitive function (Dietrich 2003) and others that will be explained later, the DLPFC exerts inhibitory control over emotional and cognitive behaviours not suited for a specific goal in a top-down manner, which is opposed by bottom-up processes of "lower" structures that superimpose highly complex computational constructs, therefore increasing cognitive flexibility. This bottom-up process is partly given by projections to the motor cortex from all levels of the

cognitive hierarchy (Dietrich 2004) and modified by neuromodulatory projects from the reticular activating system (Dietrich 2011). Similarly, frontal lobe patients are strongly acting on immediate cues (Lhermitte et al. 1986).

Next to the type of information, the brain processes information using either the explicit or the implicit system to acquire, memorize and represent knowledge (Dietrich 2004). While the rule-based explicit system can be expressed with words and is tied to conscious awareness, the implicit system is skill-based (Dietrich 2004), inaccessible to conscious awareness and its content hard to grasp in words and therefore only observable by task performance (Ashby & Casale 2002; Dienes & Perner 1999). Consequently, implicit learning is independent of conscious attempts and explicit knowledge (Reber 1993) as shown in the example of language acquisition (Schacter & Bruckner 1998) and the Tower of Hanoi, a game whose description of its solution by students is unable to read by a computer (Gazaniga et al. 1998). In contrast, the explicit system forms a mental representation that includes additional information and thus can be seen as learning-by-thinking rather than learning-by-doing. Learning skills has been shown to be represented simultaneously and complementary by explicit and implicit mental representations (Milner et al. 1968) and the degree of contribution of either system was suggested to be dependent on the amount of practice and the nature of the task (Dietrich 2004). While the nature of a task dictates the initial involvement of explicit or implicit information processing, practice is then able to shift that distribution towards the implicit system typically. The first mentioned is nicely illustrated by the Wisconsin Card Sorting Test (WCST), in which colour, number or shape determine the rules for card sorting. The verbal communication of these rules that change and have to be discovered empirically using only feedback from the examiner gets worse and ultimately impossible with increasing task complexity due to multi-dimensionality of probability (Waldron & Ashby 2001). Using a frog example Crick & Koch (1998) confirm this implicit regulation to handle increased complexity of reflexive systems, which is fast but at the same time rigid and inefficient when it comes to organization of multiple reflexes acting together to respond stereotypically, zombie-like towards visual input such as small prey. This gives the rationale for the explicit system allowing temporal buffering and holds multiple representations so that the output decision can be regulated and modified if necessary.

The explicit and the implicit system can be separated both, functionally and anatomically, as evidenced by animal and brain-damaged patients research as well as by neuroimaging studies (Schacter & Bruckner 1998; Squire 1992). The neural substrates for the explicit system are the DLPFC because its working memory buffer represents the content of consciousness and the executive attentional network, which includes the DLPFC selects the content (Ashby & Casale 2002; Dhaene & Naccache 2001) as well as medial temporal lobe structures (Poldrack & Packard 2003). More specifically, the attentional network includes parietal regions whereas the executive network mainly

involves the DLPFC. The notion that the prefrontal cortex developed phyologenically and ontogenically last (Fuster 2002) underlines the importance of the prefrontal cortex and supports the assumption of a hierarchical structure of cognition and explicit functioning in particular (Dietrich 2003), with the prefrontal cortex at its top. The origin for implicit information processing is less clear but has been suggested to be embedded in the brain circuit of the basal ganglia (Dietrich 2004), which involves the procedural memory for motor and cognitive skills and priming, conditioning and habituation (Poldrack & Packard 2003; Squire 1992). Multi-dimensional tasks are likely represented by the implicit system due to the capacity limit of the working memory (Cowan 2001), which is defined as the complexity of relations that one is able to process in parallel (Halford et al. 1998). A consequent overloading of executive capacity results in two effects. First, information collapses into fewer chunks, which are processed in a serial manner and make the information therefore temporarily inaccessible (Halford et al. 1998). Second, such an overload drives information from the explicit to the implicit processing system giving the basis for implicit or automatized learning. As it is well known in the area of artificial intelligence, the computational dimensions of a tennis serve, for example are enormous and therefore cannot be stored in the working memory, requiring focused attention on every little step (Dietrich 2004). Rather motions like that are broken up into components to focus on and then put together in an automatized manner, represented in the implicit system, which does not seem to have capacity limits. When a new movement is executed, the explicit system in the prefrontal cortex builds a time-consuming, mental representation concerning task requirements and projects to premotor cortex and primary motor cortex to execute it. This has been supported by neuroimaging studies showing activation of the prefrontal cortex, the premotor cortex, cerebellum and the parietal cortex when a new skill is acquired (Jenkins et al. 1994) whereas the basal ganglia reflects as a passive observer (Gazzaniga et al. 1998). However, when this skill gets consolidated an activity shift occurs towards the basal ganglia (Mishkin et al. 1984), supplementary motor cortex, the motor thalamus and the hippocampus (Jenkins et al. 1994), pointing towards the construct of an implicit representation, non-scientifically termed "muscle memory". In the case of a novel for running on a treadmill, the start likely impairs focused attention as prefrontal and thus executive resources as well as primary motor cortex are taken up but when the runner get used to the treadmill, the basal ganglia and supplementary motor cortex can be regarded to account for the running, which is guided by perceptual input from the parietal cortex whereas working memory and thus attention is released to attend to other cues. The beneficial efficiency of the implicit system is show by the example of Dienes & Perner (2002). The sentence "I know that this is a cat" holds the content (cat), which is the lowest level, also termed procedural knowledge, allowing a mouse to run away, the attitude (know) allowing to possess and use information in a meta-representation and determines if the first level was a fact and the holder (I). If the holder also converts to a higher-order representation, the information is regarded as fully conscious (Kihlstrom 1996). Since the implicit or procedural knowledge is cannot determine whether something is a fact or not, it is inflexible and idiosyncratic (Dienes & Perner 2002) as it cannot represent

knowledge as a hypothetical construct. However, the efficiency of the implicit system and motor skills compared to the explicit is due to absence of implicit predication, factivity and the exponentially increasing computational complexity in higher-order representations (Dietrich 2004).

Transferring informative knowledge of a skilled behavior that was acquired long ago implicitly has to proceed with the interference process (Dienes & Perner 2002; Frensch et al. 2002) and with a circuitous route of the actual behaviour to be represented consciously by the explicit system allowing buffering that event and connecting it to hypothesis testing to extract the skill´s critical elements (Dietrich 2004). Such a transformation is well demonstrated when people are dialling a phone number on an imaginary phone dial to remember a number. There is no direct bottom-up process of predicative and fact –holding implicit knowledge to the explicit system.

In an experiment of Bridgeman et al. (1997) subjects were shortly exposed to the visual illusion of a rectangular frame that moved over a computer screen creating an apparent motion of a fixed dot located inside the frame moving in the opposite direction and then asked to either verbally describe the last location of the dot or point it out with their hands. Pointing to the location, representing procedural knowledge, was quick, efficient and accurate, pointing towards a precise real time sensory-motor integration of the implicit system whereas verbal descriptions were highly susceptible to the illusion effect. The common description of top athletes "You can´t win by thinking" has interestingly been indicated in that study showing susceptibility to the Roelofs effect in both conditions when responses were withheld for 8 seconds. The finding that visually guided movement outstrips time implicit hence is rigid and inflexible has been shown in another study that looked at the switch of grasp movements of 3 rods whose illumination was the cue for the onset of the movement, which was corrected and accompanied by a vocal indication of the subjects when the illuminated rod changed (Castiello et al. 1991). The results showed that grasping of a new target often happened already before being consciously aware of it. Fast, moment to moment adjustment opposes smooth feedback-driven sensory-motor integration but together allows for instance to catch a flying ball as its location and speed estimation are continuously and stepwise updated (McLeod et al. 2001) and the higher meta-representation allows hypothetical scenarios that serve to anticipate several steps in advance (Dietrich 2004). Such moment-to-moment execution relies strongly on the implicit, reflexive loops and therefore on practice. However, real time processing of the nonlinear, dynamic explicit system has such a high number of possible next moves so that future projections would bifurcate to infinity creating an unpredictable scenario favouring a specific attractor (typically a higher goal) (Dietrich 2004). A solution would be outside real-time processing with split up parts of information. However, for optimal and skilled movements, either the number of reflexive systems and/or the number of response patterns in the reflexive system can be increased leaving modularity of a reflexive system (output guided by immediately preceding input) the same but increasing the number of specialized and independent response patterns (Dietrich 2004). In other words, team sports requiring planning,

memory retrieval or attention are prefrontal dependent whereas running in familiar surroundings is to a much lesser degree dependent on prefrontal processes. Ultimately, initial practice results in establishment of general reflexive systems while more practice would lead to a increase in the number of specific and independent response pattern within each system, similarly to the dynamical systems theory with increasing degrees of freedom and therefore allowing higher range of movement in joints. As it has been suggested that the degree of implicitness of a skill directly translates to the quality of its performance (Dietrich 2004) one could assume that a potential reduction in prefrontal function and hence explicit activity leads to performance enhancement of technical skills. With increasing internalization of a sport skill and therefore control of the basal ganglia and supplementary motor cortex the more prefrontal disengagement can be expected. The executive network to suppress an undesired motor outcome has been reviewed by Aron Robbins & Poldrack (2004) who identified the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex (ACC) and the right inferior frontal cortex (pars opercularis; rIFC) as main structures for response inhibition and hypothesized that the left-lateral PFC sets and maintains goals while the ACC detects conflicts in case the stimulus is different from those goals, and the rIFC eventually suppresses irrelevant responses.
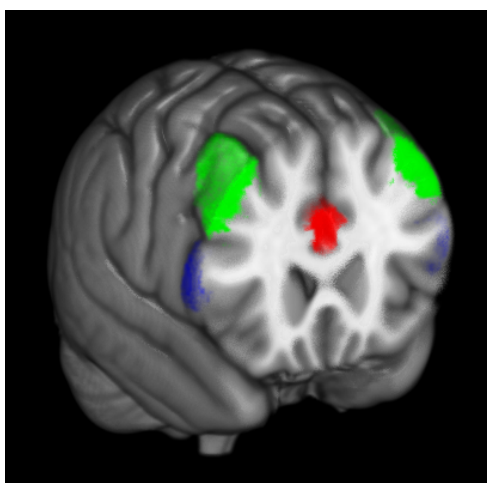
Figure 6: Executive Network suggested for Response Inhibition
Note. Areas suggested to be activated during a response inhibitory action (Aron Robbins & Poldrack 2004). Red: Anterior cingulate cortex, Blue: Inferior frontal cortex (pars opercularis), Green: dorsolateral prefrontal cortex.

1.3   Reticular-Activating Hypofrontality Theory

First, peripheral measurements of endorphins are not representative of central opioid release (Rossier et al. 1977; Dietrich & McDaniel 2004) and the study of Boecker et al. (2008) investigating central opioid release "rests on sketchy evidences" (Dietrich 2009), which is likely due to recent work by Hume et al. (2007) doubting the suitability of radiolabeled diprenorphine to detect changes in opioid binding after application of exogenous/synthetic opioid. Secondly, theories relying on more blood and thus more glucose and oxygen are also unlikely to explain psychological changes during and after running. While light and moderate exercise were shown to remain constant global blood flow, cerebral

metabolism and oxygen uptake (Ide & Secher 2000; Sokoloff 1992) strenuous exercise had been evidenced to even decrease global cerebral perfusion (Nybo & Secher 2004) and thus blood flow to the brain as a percentage of cardiac output can be regarded as constant resulting in a stable perfusion rate (around 750 ml min^{-1}).

Due to the inability of the models described so far to account for the various cognitive changes described in the literature Dietrich & Audiffren (2011) suggest the reticular-activating hypofrontality (RAH) model to explain specific changes occurring during an acute bout of exercise. This model bases on the assumption of a transient decrease in prefrontal and possibly limbic structure activity during exercise, which is both, paired and counteracted by reticular activating processes (Dietrich 2003) described above. This activity decrease happens in the order of the hierarchical organized level of consciousness as depicted in figure 7 with the prefrontal cortex at the top of the consciousness level (Dietrich 2003) but not ultimately necessary for it (Bogen 1995) and therefore regarded as the highest-order of consciousness. Decreased frontal cortex activity has been suggested to be due to the computation demand of bodily motion, a finite energy supply and competitive neural processing (Dietrich 2009; Dietrich 2003; Dietrich 2004; Dietrich 2006; Dietrich & Audiffren 2011) which all lead to an inability of the brain to maintain activation in all its networks, consequently reducing activity in those brain areas that are not directly necessary to maintain exercising. First, real time sensorimotor integration, particularly facing the challenge of balance makes it extremely demanding for the brain to control and synchronize a large amount of muscle fibers, especially considering that every twitch affects the contraction of the next one in a time dependent manner (Dietrich & Audiffren 2011). Second, the motor structures involved in movements, such as the primary motor cortex, secondary motor cortices (premotor and supplementary motor area), basal ganglia, the motor thalamus, cerebellum, red nucleus, substantia nigra (see figure 8), the massive pathway systems an the motor neurons in the spinal cord, among even more represent almost the entire brain and a very high number of neurons, especially considering the cerebellum (Dietrich 2009). Several studies support this activity pattern by looking at functional activity of neurons in animals using cerebral blood flow (CBF) and local cerebral glucose utilization (LCGU) (Holschneider et al. 2003; Sokoloff 1992; Vissing et al. 1996). Using local LCGU, Vissing et al. (1996) confirmed this by finding similar wide spread activation patterns in cerebral grey matter structures involved in motor, sensory and autonomic function, together with white matter structures in the cerebellum and corpus callosum in rats running for 30min at 85% maximal volume of oxygen uptake. Consequently, prolonged exercise would require sustained activity in those regions (Dietrich 2006). Interestingly, besides the significant increase in LCGU in all brain structures, there was no such increase in prefrontal cortex, frontal cortex, cingulum, CA3, medial nucleus of the amgydala, lateral septal area, nucleus accumbens, some hypothalamic nuclei, median raphe nucleus, interpeduncular nucleus, nucleus of the solitary tract and inferior olive. In addition, movement occurs in space requiring sensory input integration and hence enlarging the list

of brain structures involved in movement. Third, the brain capacity for information-processing limited at the bottleneck of consciousness and also the total amount of information processing unconscious and parallel is restricted by a fixed amount of metabolic resources. The resulting transient need-based shift of brain activation is well known in functional neuroimaging studies and indicated in a rat model during treadmill running, showing decreased CBF-TR in the primary somatosensory cortex mapping jaw, oral regions and the barrel field, which implies redistribution of resources away from these areas (Holschneider et al. 2003, p. 929). In evolutionary terms re-allocation of neural resources, which according to Dietrich (2009) also happens other situations taxing the brain and compromising brain integrity such as thermal challenges, starts from top to down because cognitive function has been described as hierarchically ordered and decreasing top-down control allows increased behavioural flexibility and adaptability. In other words, acting on instinct in a situation that is physically straining the body reduces processing time and might therefore be important for survival. The competitive nature of the brain to process information (Dietrich 2007; Miller & Cohen 2001) with its access to consciousness (Crick & Koch 1998) adds up to the limited information processing capacity due to finite metabolic resources. Dietrich (2003) describes frontal hypofunction during prolonged physical exercise as "timelessness, living in the here and now, reduced awareness of one´s surroundings, and diminished analytical or attentional capacities" – similar to the mentioned experience of the "runner´s high".
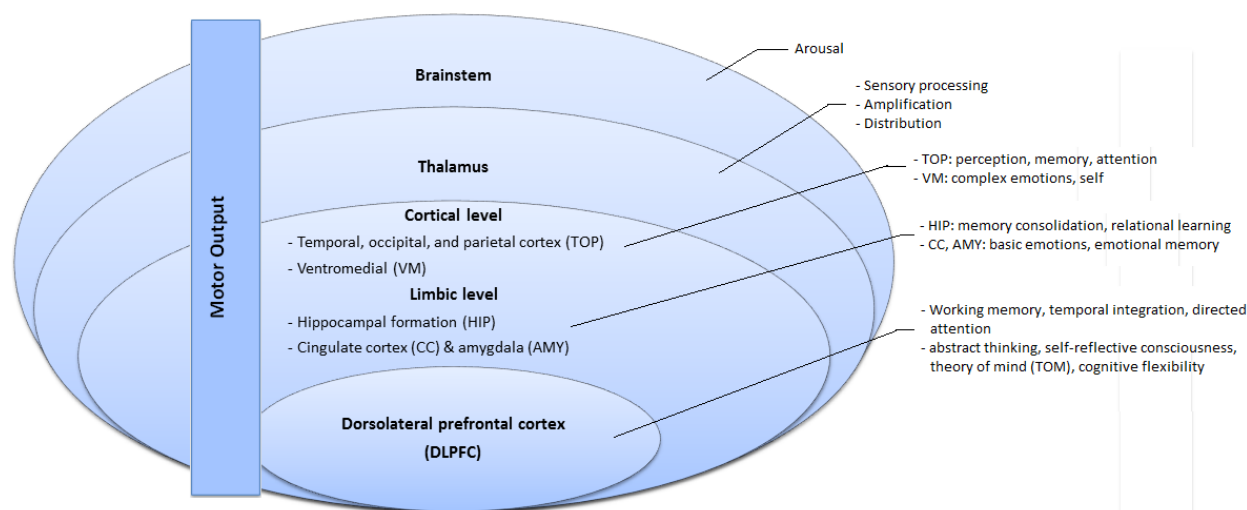
Figure 7: Hierarchy of Consciousness
Note. The dorsolateral prefrontal cortex is suggested to be at the top of consciousness by integrating already-processed information from lower brain areas in a high computational manner. The ventral medial prefrontal cortex, together with temporal, occipital, parietal cortex and the limbic system involving the hippocampus, cingulate cortex and the amygdala serve as inputs to the highest cognitive centres. The brainstem is considered to be on the bottom of this hierarchy but plays an important role in arousing the system with specific projections. The thalamus processes information further, amplifies it and serves as a major distributor to the appropriate areas. All levels have access to motor output, adapted and modified from Dietrich (2003).

In humans, functional magnetic resonance imaging (fMRI) is neither adequate to map neural activation during exercise nor sufficient to detect changes following exercise due to the high temporal association of a task to brain activation, pointing towards an immediate normalizing effect of exercise-induced changes. However, a PET study that used cycling showed increased activation in the primary sensory, cortex, primary motor cortex, supplementary motor cortex and anterior part of the cerebellum (Christensen et al. 2000) while during walking increased regional cerebral blood flow (rCBF) was elevated in the supplementary motor area, medial primary sensorimotor area, the striatum, visual cortex and the cerebellar vermis in a single photon emission computed tomography (SPECT) study (Fukuyama et al. 1997). The differences in activation patterns compared to animal studies are at least in part likely due to the necessity of keeping the head still, which is not in line with an optimal challenge of the resources of motion given by muscle mass, exercising intensity and duration (Dietrich 2009). The poor temporal resolution of PET using 18-fluorodeoxyglucose (^{18}FDG) can serve to see brain activation during exercise since glucose uptake occurs late and is not readily metabolized by neurons, allowing the scanner to estimate regional changes later as glucose stays fixed long enough. Using this technique, massive brain activation has been shown as a function of large-scale body movement (Kemppainen et al. 2005; Tashiro et al. 2001). More particularly, Tashiro et al. (2001) found general cortical deactivation, especially obvious in prefrontal regions and this prefrontal hypometabolism was associated to fatigue (Kemppainen et al. 2005). EEG studies indicate an association between exercise and alpha and theta enhancements, primarily in the frontal cortex (Kubitz & Pothakos 1997; Nybo & Nielsen 2001) reflecting decreased brain activation. Petruzzello & Landers (1994, p. 1033) concluded in their EEG study a decrease in right frontal activation after exercise, which was in a cat EEG study shown to gradually go back to pre-running brain activity within 11 minutes (Ángyán & Czopf 1998) and Nybo & Nielsen (2001) not only confirmed a link between exercise and decreased frontal activity doing a stepwise forward-regression analysis of the frontal, central occipital placed electrodes but also found that rate of perceived exertion is best predicted by frontal deactivation. Single cell recording of 63 neurons in the prefrontal cortex demonstrated specific changes in discharge with increasing rates in those units associated with movement control and decreased discharges in other prefrontal units (Criado et al. 1997). Even though there is less evidence of reduced activity in limbic regions, the RAH model has been proposed to have anxiolytic and antidepressant effects by inhibiting excessive neural activity in the prefrontal cortex (Dietrich & Audiffren 2011), which has been associated with anxiety and depression disorder (LeDoux 1996; Mayberg 1997, respectively). Moreover, the RAH model seems to be the only model being able to explain the mood enhancing effect during aerobic exercise, which does not occur during anaerobic exercise (Dietrich 2009). In summary, the RAH model suggests that large-scale bodily movements involve a massive and prolonged neural activation in sensory, motor, and autonomic systems, which, due to a fixed amount of metabolic resources (Ide & Secher 2000) and the competitive brain processing (Miller & Cohen 2001), comes at the cost of structures not directly involved in maintaining

those movements such as the higher cognitive centres of the frontal cortex (Dietrich & Audiffren 2011).
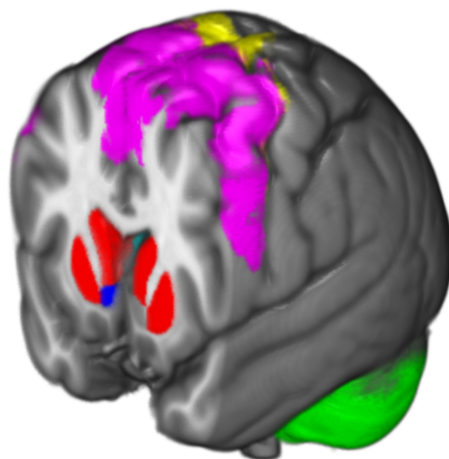
Figure 8: Brain Areas active during exercise
Note. Cerebral blood flow and local cerebral glucose utilization studies (Holschneider et al. 2003; Sokoloff 1992; Vissing et al. 1996) confirm the brain activation pattern during exercise suggested by Dietrich (2003). Green: Cerebellum, Purple: Primary Motor Cortex, yellow: Premotor and supplementary area, Red: Caudate, Putamen, Pallidium, Blue: Nucleus Accumbens, Turquoise: Red Nucleus. Particularly interesting in comparison to the suggested activity an executive cognition task depicted in table 6.

On a behavioural level the strongest support for the RAH model was evidenced by Dietrich & Sparling (2004) who found a decline in performance in cognitive tasks requiring a large amount of prefrontal activation and Cian et al. (2000) who found a dramatic temporary impairment of cognitive performance close to total physical exhaustion. Laboratories that have been reporting arousal effects at early stages of exercise also started documenting cognitive impairment in executive tasks (McMorris et al. 2008b), which was suggested to be due to absent labelling of implicit or explicit tasks (Dietrich 2009). While implicit processes, mostly measured as simple or choice reaction time, seem to be enhanced in cycling studies (Paas & Adam 1991; Adam et al. 1997; Arcelin et al. 1998; Davranche & Audiffren 2004; Davranche et al. 2005; Davranche et al. 2006; Audriffen et al. 2008) explicit processes, such as short-term memory (Paas & Adam 1991; Adam et al. 1997) assessed by the WCST (Dietrich & Sparling 2004), Paced auditory serial addition task (Dietrich & Sparling 2004), Ericksen

flanker task (Pontifex & Hillman 2007; Davranche & McMorris 2009) or the Vigilance task (Mahoney et al. 2007) seem to be impaired. This supports the model described by the RAH model (Dietrich & Audriffen 2011) stating the brain shifts its metabolic resources to drive the motor neurons leading to impaired consequences within minutes (Kemppainen et al. 2005; Tashiro et al. 2001) for those neurons not directly involved in the computation of exercising. The resulting hypofrontality state not only inhibits activity in the explicit system due to lack of resources in prefrontal brain areas but also disinhibits implicit information processing (Dietrich 2009). Together with and as a consequence of the arousal system in the brainstem (reticular activation) this leads to up-regulation of neurotransmitter systems (Dietrich & Audriffen 2011). As motor neurons maintain high firing rates due to the physical activity the brain reaches a metabolic hole, which is expressed in a down-regulation of neural networks along the functional hierarchy of cognitive control.

While the temporal, occipital and parietal lobes (TOP) are mainly involved in perception, learning and memory and their association cortex further assembles and assimilates sensory information, the frontal lobe, located rostal of the central sulcus, which demarcates the frontal lobe from these three posterior cortices, is primarily involved in executive function by integrating perceptual information, designing plans and strategies for appropriate behaviour and projecting to adjacent motor cortices for the execution of its computational product (Dietrich 2003). Moreover, the frontal cortex enables even higher cognitive functions, such as self-construct (Keenan et al. 2000), self-reflective consciousness (Vogeley et al. 2001), complex social function (Damasio 1994), abstract thinking (Rylander 1948), cognitive flexibility (Lhermitte et al. 1986), willed action (Frith & Dolan 1996) and theory of mind (Frith & Frith 2001) as well as plays a central role for working memory (Fuster 2000a), temporal integration (Knight & Grabowecky 1999) and both, sustained and directed attention (Sarter et al. 2001). Thus the prefrontal cortex allows computation of complex cognitive functions by providing a buffer to hold information and attribute it in space and time (Dehaene & Naccache 2001). The prefrontal cortex is functionally divided into ventromedial and dorsolateral prefrontal cortex (VMPFC; DLPFC, respectively), which have no global functions of the prefrontal cortex but rather have discernible hemispheric specializations. For example, left DLPFC mainly accounts for semantic memory whereas the right DLPFC deals with sustained attention (Duncan & Owen 2000). The famous case of Phineas Gage, who had a frontal lobe lesion after a freak accident, indicates symptoms of a typical frontal syndrome: inappropriate social behaviour, no social inhibition, little abstract thinking, no planning of future, little moral judgment and/or difficulties to maintain a plan of action. While the VMPFC with its intrinsic connections to the limbic system has been suggested to judge consequences of one´s behaviour for which emotional changes serve associate with logical and rational decisions (Damasio 1994), the DLPFC is crucial for directed attention, temporal integration, and working memory (Fuster 2000a; Knight & Grabowecky 1999), whose buffer is necessary for cognitive flexibility, abstract thinking, strategic planning, access to memory and sentience but not personality

and emotions. Damage to the DLPFC has most reliably been related to perseverance, the inability to shift between modes of thinking (Brauer Boone 1999), pointing towards lack of flexibility and abstract thinking. This has been investigated using the Wisconsin Card Sorting Task (WCST), in which cards are sorted by colour, number or shape and rules for sorting have to be found out by empirically using feed from the examiner and by a study using a T-maze, in which rats have to shift strategies to get to the food source (Dietrich et al. 2001). This study found that animals persevered and adhered to the "old" rule. Interestingly, Lhermitte et al. (1986) documented that frontal lobe patients reacted on what they see without selecting behaviours based on a more universal picture and non-scientific observation also implies maladaptive emotional behaviour during sports, possibly due to a disengagement of the prefrontal cortex. Lesions to lower levels of consciousness such as the mesencephalic reticular formation wipes out consciousness altogether (Dietrich 2003). The thalamus, which processes information separately and parallel representing the hippocampal formation, as well as the TOP cortices, regulates what reaches consciousness involving the binding experience (Llinás & Paré 1991), processing of perceptual information via the LGN and amplification of information (Crick 1994). Its reciprocal projections to the neocortex and the limbic system allow distribution of information to the right places for further processing (LeDoux 1996), which permits further perceptual information processing, storing of computation as memory and requires selective attention (Dietrich 2003). Since the cognitive construct cannot involve unprocessed and not already computed information in the prefrontal modules for computation of higher cognitive functions, the higher the lesion the more selective the deficit. At the top of this hierarchy is the frontal cortex with the DLPFC as evidenced by Damasio (1994) showing that damage to the VMPFC had no negative effects on hypothetical situations of complex social and moral dilemma whereas the damage to the DLPFC impairs abstract thinking and hence the maximal capacity of consciousness. Working memory, temporal integration and focused attention are regarded as global capacities of frontal tissue (Dietrich 2003), providing the computation basis for further, higher cognitive processing. Moreover, the buffer of working memory has been suggested to hold the current conscious awareness (Baddeley 2000) and the access for motor system activation from all levels in the hierarchy has been rationalized from an evolutionary point of view (Dietrich 2003). To sum up the prefrontal cortex function, it seems that this evolutionary newer structure does not suppress input from "lower" centres but rather modulates that input in a more sophisticated manner. Hence loss of function is simply overtaken by the lower structures that can trigger motor output.

1.4   Central Fatigue

Among athletes who run marathons the term "hitting the wall" is quite commonly known and describes a state in which exercise intensity cannot be maintained, feels very exhaustive and the drive

to exercise is lost. This is interestingly, opposed to the mentioned state of "runner´s high" when lightness and a flow in experienced. Chaudhuri & Behan (2004) defined central fatigue as the "failure to initiate and/or sustain attentional tasks and physical activities requiring self motivation", thus implying a cognitive component. However, an association between cognitive decrements and central fatigue could not be shown yet and have mostly addressed multiple sclerosis patients (Leawitt & DeLuca 2010).

While the brain activates the muscle, the muscle acts as a potent competitor for continuous oxygen and substrate delivery. Ross et al. (2007) evidenced central fatigue, relative to the neuromuscular junction after a marathon run. Further, central fatigue has been associated particularly with slow muscle contractions during intense exercise of short duration, accompanied by reduced oxygen tension in the brain (Rasmussen et al. 2007a) but can, however, not be predicted by elevated brain temperature or low blood glucose levels (Nybo & Secher 2004). Even though low glycogen stores and high serotonin/tryptophan levels have been proposed mechanisms triggering central fatigue remain unknown. Central Fatigue might serve the purpose to protect vital bodily functions.

Declines in running speed are generally linked to muscle glycogen depletions requiring different activation strategies because an impaired running style points towards impaired activation. In their study, Ross et al. (2007) used transcranial magnetic stimulation (TMS) for twitch interpolation to express the central activation efficacy in recruited muscles. Compared to the measurement of voluntary activation with electrical stimulation of the motor nerve (Merton 1954), which might also stimulate the peroneal nerve and hence activate peroneal muscles next to the aimed tibialis anterior muscle making ankle joint torque interpretations difficult, using TMS for twitch interpolation (Todd et al. 2003) is an adequate technique to evaluate muscle fiber recruitment. Particularly, triggering tibialis anterior with TMS has the advantage of a low threshold of that muscle compared to the anagonist (soleus muscle), which is beneficial when stimulus driven force is compared to voluntary effort. Even though voluntary activation was less than 90% of the TMS-triggered strength (this is also lower than reports of electrical stimulation studies) treadmill marathon running reduced the muscle´s ability for maximal performance (Ross et al. 2007). In contrast to twitch interpolation technique studies investigating central fatigue (Gandevia et al. 1996) voluntary activation of the tibialis anterior muscle was reduced within 20min after exercise up to 4h after running. In conclusion the study of Ross et al. (2007) clearly showed reduced central drive after marathon running. However, the mechanisms underlying such a reduction are unclear. First, ammonia might act as a fatiguing agent. Due to enhanced neural metabolism cerebral blood flow to the brain increases and the ratio between cerebral metabolic rates of oxygen (CMR_{O2}) and carbohydrate (CMR_{CHO}) shifts from a rest value of about 6 towards increased carbohydrate uptake relative to oxygen (Dalsgaard 2006). Elevated cerebral metabolism during exercise is mirrored by a reduced ratio and taken into consideration that the brain has limited capacity for anaerobic metabolism one can assume that the surplus carbohydrates taken up

are metabolized, even though ammonia clearance might account for as much as 10% of the surplus carbohydrates taken up (Dalsgaard 2006). Absence of an effective urea cycle in the brain ties neurons to the dependency on glutamine synthesis from glutamate to remove ammonia released by the muscles and taken up by the brain during exercise (Rasmussen et al. 2007b). A consequent of ammonia elimination is that glutamate and γ –aminobutyric acid (both excitatory neurotransmitters) get reduced and hence cause a cerebral dysfunction and hence chronic fatigue, as in hepatic diseases (Nybo & Secher 2004). Second, differences in serotonin, an important neurotransmitter for regulating arousal, sleepiness and mood whose kinetics are usually assessed with its precursor tryptophan have been suggested for an important trigger of central fatigue (Rasmussen et al. 2007b). Moreover, dopamine, which is involved in controlling movements and its metabolism enhanced during exercise in animals showed increased arterial concentrations during strenuous exercise but no change in release across the brain was reported (Nybo & Secher 2004). More theories include dysbalance in immune system, reduced nerve conduction, neuroendocrine and neurotransmitter impairment as well as energy depletion theories. In detail, neural metabolism might be affected by proinflammatory cytokines or the hypothalamic-pituitary-adrenal axis. Chaudhuri & Behan (2000) identify the basal ganglia as the main structure for central fatigue with its six interconnected nuclei projecting to the limbic system via amygdalostriate connections from the basal lateral amygdaloid nucleus as well as afferent and efferent projections and feedback connections to the prefrontal cortex and links to the hypothalamus. Disorder associated with central fatigue, such as Parkinson, multiple skelerosis, postpolio syndrome and depression support the importance of the basal ganglia and its connection between prefrontal cortex and thalamus. Moreover, lesions in the basal ganglia impaired limbic integration for cortically driven voluntary activities (Nauta 1986). Using positron emission tomography an association was found between MS patients reporting fatigue and hypometabolism in the prefrontal cortex, putmamen, premotor cortex and right supplementary motor area (Roelcke et al. 1997). Further, comparing MS patients with fatigue and those without using fMRI indicated reduced functional cerebral activation in brain regions for motor planning and execution such as ipsilateral precuneus, ipsilateral cerebellar hemispheres, contralateral middle frontal gyrus and contralateral thalamus (Filippi et al. 2002). Interestingly, when looking at a cognitive task that measures sustained attention (modified Symbol Digit Modalities Task) MS patients had an increase in brain activity across time in orbitofrontal cortex, superior parietal cortex, and the caudate in the basal ganglia compared to controls who had a decrease in brain activity (DeLuca et al. 2008). Since accuracy was not different, this finding point towards a greater neuronal effort to sustain task goals and might underline that greater wide spread neural activation might relate to central fatigue similar to the assumption of a high neural activation during exercise leading to hypofrontality (Dietrich 2003). Similarly, TBI patients showed greater neural activation compared to healthy controls during a cognitive task in the basal ganglia, middle frontal gyrus, superior parietal cortex, and anterior cingulate (Kohl et al. 2009).

	Peripheral Fatigue	**Central Fatigue**
Gandevia et al. (1996)	Any exercise-induced reduction in the ability to exert muscle force or power, regardless of whether or not the task can be sustained	A progressive exercise-induced reduction in voluntary activation of a muscle
Chaudhuri & Behan (2000)	The inability to sustain a specified force or work rate because of physical limitations of the muscles, nerves or cardiovascular system but little loss of endurance in mental tasks; thus, peripheral fatigue is associated with physical but not mental fatigue	The failure to initiate and/or sustain attentional tasks and physical activities requiring self motivation (as opposed to external stimulation)
Wessely et al. (1998)	Muscle fatigue: a decrease in the force generated by muscles during a repeated neuromuscular task. A progressive exercise-induced reduction in voluntary activation of a muscle	Fatigue that has its source at the level of the upper motor neuron or above (eg, above the neuromuscular junction)

Table 1: Definitions of peripheral and central fatigue
Note. The distinction between peripheral and central fatigue has been addressed in several papers and forms a research area. The table summarizes the current opinions and definitions of authors concerning central and peripheral fatigue, adapted from Leavitt & DeLuca (2010).

1.5   Hypothesis

The current study aimed to investigate effects of exercise intensity on executive function in young, healthy adults[#] using the Conners Continuous Performance test whose performance variables are described in table 2. The CCPT test has never been used in an exercise setting before but is very valuable with regards to realistic, every-day situations, which no do not only involve one information processing system but rather the whole network. In a second part of the study, cognitive performance was similarly assessed and tried to be altered and modified using non-invasive electromagnetic techniques. Given the current state of the literature we hypothesized that

1. Treadmill exercise affects executive function during exercise.

2. Executive function* during exercise is differentially affected by low and moderate intensity exercise.

3. Treadmill exercise affects post exercise executive function*.

4. Post exercise executive function* is differentially affected by low, moderate and high intensity bouts of exercise (that are isocalorifically equal).

5. Treadmill exercise positively / negatively affects post exercise mood.

6. Mood is differentially affected by low, moderate and high intensity bouts of exercise (that are isocalorifically equal).

* NB. Executive function will be further sub divided into three different aspects of executive function we will assess using the CCPT test ie focus, impulsivity and sustained attention (more details in the methods section below); therefore there will be further sub hypotheses within hypotheses 1. – 4.

It may also be possible to detect group differences within this population although this is not a primary goal of the study. For example gender differences, male (n=15) vs. female (n=15) and the effect of differences in aerobic fitness (VO_2 max).

CPT-II Scores	Type of Deficit	Description
Omissions	Inattention	Omissions are non-targets that the subject failed to respond to (i.e., failure to respond to all other letters except "X"). Although these may indicate severe difficulties, questions about the validity of the administration should be raised when T scores are above 100 (e.g., partially completed test, random responding, misunderstanding directions).
Commissions	Inattention or impulsivity	Commissions are targets ("X") that the subject erroneously responded to.
Hit RT	Inattention (slow); impulsivity (fast)	Reaction time to all non-"X" letters over all six time blocks, recorded to nearest millisecond and log transformed; high T scores indicate long response times.
Hit RT SE	Inattention	Log transformed; consistency of response times as measured by the standard error for responses to targets.
Variability	Inattention	Log transformed; measure of response time consistency calculated as the standard deviation of the standard error values for each sub-block.
Detectability	Inattention	Provides information on how well the examinee discriminates between targets and nontargets (i.e., signal and noise).
Response Style	Impulsivity	This score provides a measure of the examinee's response style (e.g., cautious versus risk-taking) expressed as a function of speed/accuracy trade-off (e.g., a tendency to respond very cautiously may ensure no commission errors are made, but at the cost of missing some targets). Higher Beta values indicate a more cautious response style.
Perseverations	Inattention	A response in which reaction time was less than 100 ms; these responses are assumed to be anticipatory, perseverative, random, or slow/inattentive (i.e., carried over from the previous response) because it is physiologically impossible to respond accurately in so short a time.
Hit RT Block Change	Inattention; vigilance	Slope generated by regression analyses using block as the independent variable and HRT and SE as the dependent variables (log transformed). Positive values indicate improved reaction time as the test progresses; high T scores indicate decreased vigilance over time.
Hit RT SE Block Change	Inattention; vigilance	Log transformed; positive values (i.e., a high T score) indicate less consistent reaction time as the test progresses; negative values indicate increasingly consistent reaction times as the test progresses.
Hit RT ISI Change	Inattention	Slope generated by regression analyses using ISI as the independent variable and HRT as the dependent variable (log transformed); assesses the ability to adapt to changing interstimulus intervals; positive values (high T scores) indicate that reaction times increased as the ISI increased; negative values indicate that reaction time decreased as the ISI

		increased.
Hit RT SE ISI Change	Inattention	Slope generated by regression analyses using ISI as the independent variable and HRT SE as the dependent variable (log transformed); positive values (i.e., a high T score) indicate less consistent reaction times during longer ISIs; negative values indicate increasingly consistent reaction times during longer ISIs.

Table 2: CCPT Performance Variables
Note. The Conners Continuous Performance Test assesses 12 different performance variables in its 14min duration length. These variables can be summarized as inattention, impulsivity and vigilance. These were also the variables used for the statistical analyses, adapted and modified from Strauss, Sherman & Spreen 1998.

2   Material and Methods

2.1   Subjects

Thirty (n=30) healthy, young subjects in the age between 18 and 35 (24.27y ± 3.34y), consisting of 15 male and 15 female were recruited for the study by hanging out posters in the student`s local fitness centre at Gløshaugen in Trondheim, Norway and by sending an E-mail with the study description around the e-mail list of the medicine students of the medicine faculty in Trondheim (see Appendix A). Therefore all volunteers were students. Inclusion criteria were age (18-35) and a normal sleeping rhythm during the time course of the study because cognitive function was shown to differ between young and elderly (Conner 2003) and sleeping (Conner 2000). Exclusion criteria involved history of heart conditions, caffeine usage or brain disorders (neurological or psychiatric). Each volunteer reviewed and signed a consent form (see Appendix B) that got approved by the human research committee in Midt-Norway (REK) (see Appendix C) before participating in the study. During the study, 1 subject dropped out without completing neither the during nor the post tests due to personal reasons not related to the study. However, by recruiting one more volunteer, this subjected could be compensated for. Two more subjects could not finish all post tests (just 2 and 0) due to travelling to another country and had therefore to be excluded from the post test analysis. Another subject had to be excluded from the post test analysis because of higher values in preservation errors in the CCPT test than the limit (20) was set. This most likely implies that that subject did not react on the letters as instructed but instead just clicked randomly on what was coming up, which was supported by the high amount of omission errors. In conclusion, variables of 30 volunteers were obtained for analysis of the during sessions whereas 27 volunteers could be analysed for the post training sessions. The height, weight, maximal aerobic capacity (VO_{2max}) and maximal heart rate (HR_{max}) of the 30 and 27 volunteers were 176.53cm ± 9.30cm, 70.91kg ± 10.98kg, 54.90 ml∗kg-1∗min-1 ± 7.67 ml∗kg-1∗min-1, 194.47∗min-1 ± 6.50∗min-1, 177.48cm ± 9.28cm, 72.02kg ± 10.98kg, 54.96 ml∗kg-1∗min-1 ± 8.00 ml∗kg-1∗min-1 and 193.78∗min-1 ± 6.00∗min-1, respectively (see table).

	Minimum	Maximum	Mean	Std. Deviation
Age	19	33	24.27	3.34
Height	161	193	176.53	9.3
Weight	49.9	94.5	70.91	10.98
VO_{2max}	39.2	70.3	54.9	7.67
HR_{max}	184	210	194.47	6.5

Table 3: Information of Participants for the During Running Phase
Note. The table summarizes age, height, weight, VO_{2max} and HR_{max} of the 30 volunteers in the during running phase of the study.

	Minimum	Maximum	Mean	Std. Deviation
Age	19	33	24.56	3.3
Height	161	193	177.48	9.28
Weight	49.9	94.5	72.02	10.98
VO_{2max}	39.2	70.3	54.96	8
HR_{max}	184	207	193.78	6

Table 4: Information of Participants for the Post Running Phase
Note. The table summarizes age, height, weight, VO_{2max} and HR_{max} of the 30 volunteers in the post running phase of the study.

All subjects were healthy at the time of the testing. Subjects were treated in accordance with the Helsinki declaration.

2.2   Material and Baseline Testing

All measurements and training sessions to test the effect of exercise intensity on executive function and mood were held in the same environment in the training laboratory at the St. Olav hospital in Trondheim, Norway. A treadmill (Technogym Runrace, Italy) was used for all treadmill running exercises. Weight was assessed with a digital weighing scale (Guangzhou Yimaijia Metal Products Co) and measurement of height involved a simple wall mounted stadiometer (KWS Medical Supplies, Washington, United States).

All measurements to obtain VO_{2max} were obtained using the Oxycon Pro (Oxycon Pro, Erich Jaeger GmbH, Hoechberg, Germany) with a mouthpiece which is connected to the volume transducer, together with a tube that collects samples of the gas concentration every 10s. Prior to all VO_2 measurements the equipment was calibrated with a 3-1 standardized calibration syringe (Hans Rudolph Jäger GmbH, Germany) and the gas concentration sensor is calibrated with ambient air and a chemically standardized calibration gas with 16.0% O_2, 4.0% CO_2 and 80% Nitrogen (SensorMedics Corporation, USA).

Figure 9: Participant doing a VO$_{2max}$ test

The Oxycon pro has been validated against the classic Douglas bag technique (Foss & Hallén, 2005). Overall, oxygen uptake measured by the Oxycon pro was 0.8% (which was equal to 0.03l x min^{-1}) below the Douglas bag technique with a coefficient of variation of 1.2% (n=802). In time trials Oxycon pro showed 0.5% (0.02l x min^{-1}) lower values at 5minutes and 1% (0.05l x min^{-1}) lower values at 25min. However, the difference decreased from 1.1% to 0.5% after 3 months of testing, showing that this computerized metabolic system with mixing chamber is an accurate way of measuring VO$_2$ dynamics, involving VO$_{2max}$. Another study (Rietjens et al. 2001) confirmed this conclusion by showing that there was no significant difference between the Oxycon pro and the Douglas bag technique for minute ventilation, oxygen uptake and CO expiration in 12 highly trained subjects cycling on both, low and high intensity. Moreover, Bland and Altman analysis of validity revealed minimal bias and low standard deviations. To obtain the VO$_{2max}$ value, volunteers ran on the treadmill for 10 minutes at 7km/h at 5% inclination to ensure that they were warmed-up, a large part of the blood volume was circulating and the muscles were warm to extract O$_2$ optimally, put in the mouthpiece and then inclination was raised up to 10% in 0.5% increments every 0.5 minute. If VO$_{2max}$ was not achieved until then, speed was increased by 1km/h every minute until subjects reached exhaustion within 4-6 minutes is enough to reach maximal aerobic capacity. The achievement of VO$_{2max}$ was taken when VO$_2$ levelled off, despite further increases in running speed or inclination and when the respiratory exchange ratio (R) reached at least 1.08 (see figure 10).
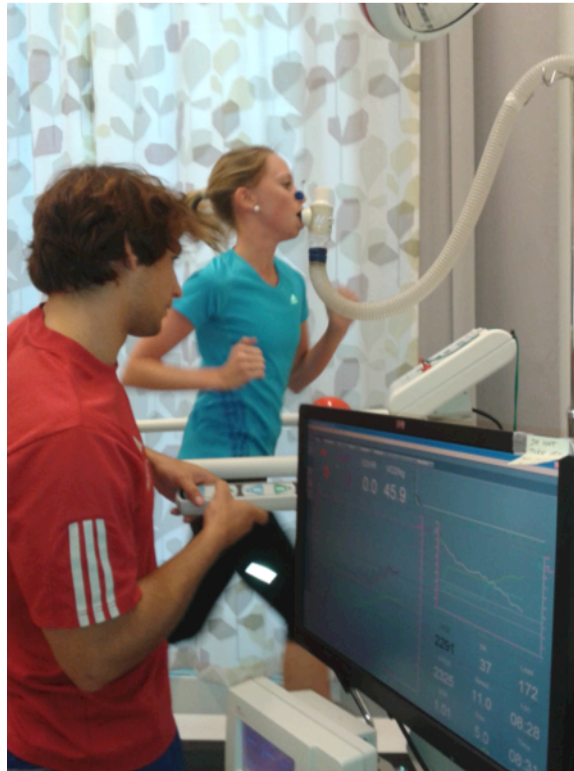
Figure 10: Assessment of VO$_{2max}$

The highest heart rate (HR) during the last minute was estimated as HR$_{max}$. For the measurement of HR, Polar Accurex heart rate monitors were used (Polar Electro, Finland). For all further training sessions, Treadmill exercise workload was adjusted based on heart rate at a given %VO$_{2max}$ which was shown not to be affected by training in a heterogeneous population with different initial VO$_{2max}$ values and an age range exceeding the one in this study (Skinner et al. 2003).

Conners´ Continuous Performance Test (2nd ed.; CCPT-II Version 5 for Windows; Conners, 2003) was used to assess response inhibition as well as (sustained) attention (Ballard 2001, Egeland & Kovalik-Gran 2010) in a resting state prior to the VO$_{2max}$ test and in separate sessions during two intensities and 5 minutes after running on three different intensities. Volunteers were instructed to click the handheld USB Trackball and 2 Buttons PC Notebook mouse button (Digiflex, Wickford, UK) during and the standard mouse when sitting as soon as any letter from the alphabet except the letter "X" popped up (see figure 11).
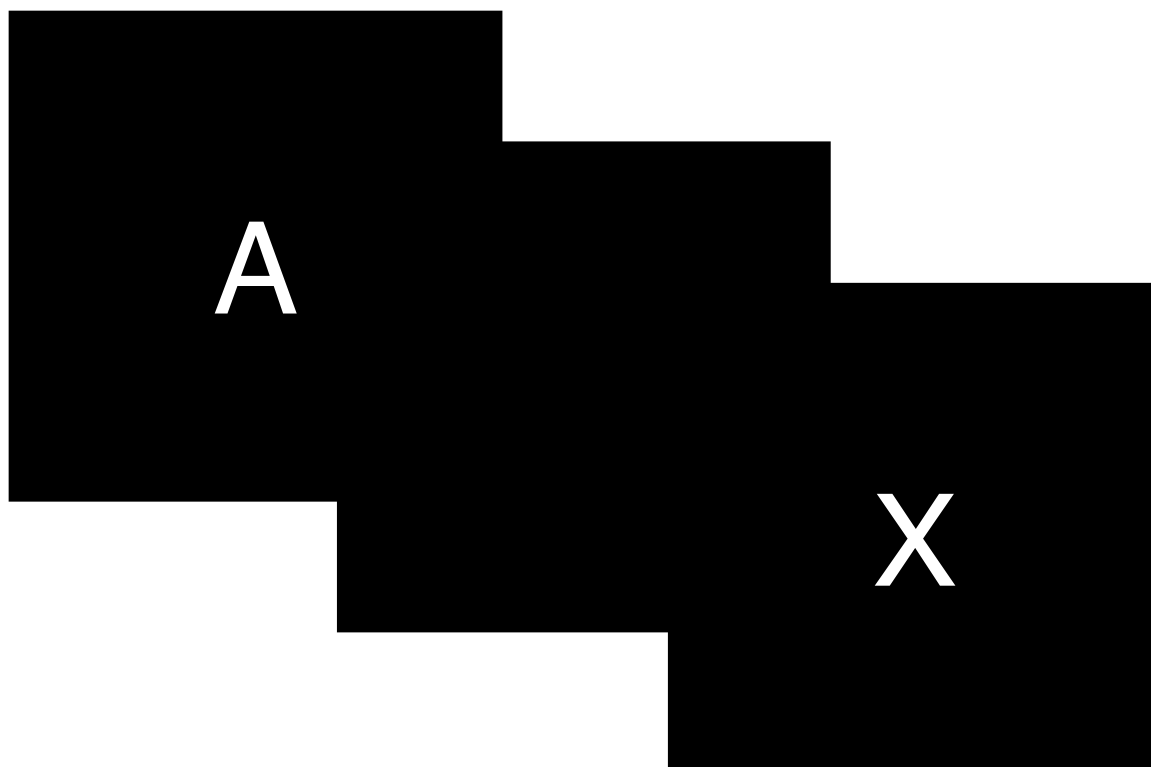
Figure 11: Computer Screen Output of CCPT assessment
Note. The pictures are chronologically ordered. The letter A was presented for 250ms and required a normal mouse button click. The empty, black screen was presented for either 1, 2 or 4sec. When the letter X was presented, subjects were instructed to inhibit their response.

The probability for the occurrence of the letter "X" was 10% and the Interstimulus Intervals (ISIs) consisted of 1, 2 and 4 seconds with a display time of 250 milliseconds. There are 6 blocks in total, with 3 sub-blocks containing 20 letter presentations and either one of the ISI each (see figure 12). Therefore the number of subblocks whose order was pseudorandomized was 18. The visual targets and non-targets are randomly shown.

Figure 12: Distribution and ISI for letter presentation
Note. The Conners Continuous Performance test consists of 6 big blocks. In each block letters are presented with an Interstimuli interval of either 1, 2 or 4 seconds. Each of this different ISI presentations consisted of 20 letter presentation of which 10% were X´s. The occurrence of the X´s was pseudorandomized.

Prior to each CCPT test in this study participants were instructed by the test supervisor to:

> *"Click once for each letter except the letter X. Respond as quickly and accurately*
>
> *as possible throughout the whole test."*

A short practice test of 70 seconds prior to the main test whose performance was used for the statistical analysis was used to familiarize the participants with the paradigm. The standardized instructions were presented on the screen and also repeated briefly by the examiner. During the test the examiner stayed in the room but remained unobtrusive. Performance Tables for each block and the different ISIs got provided by a computer-generated report at the end of the test that was not accessible for the volunteers. The whole test took 14 minutes to complete (see figure 13).
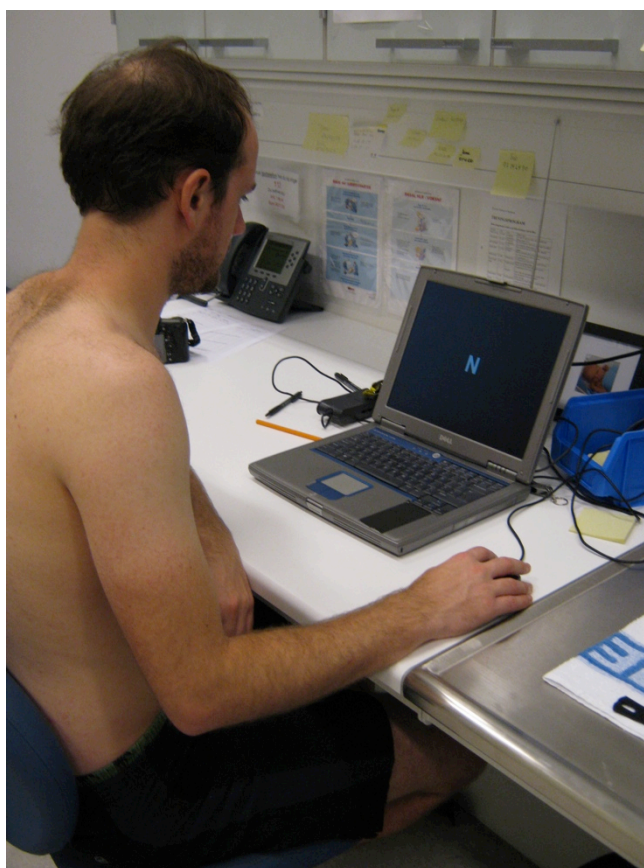
Figure 13: Assessing Executive Function Post Running

The table 5 depicts the performance measures of executive function that were chosen to investigate (focus, impulsivity and sustained attention) and can be assessed from the CCPT data (Egeland & Kovalik -Gran 2010).

Focus	*Impulsivity*	*Sustained attention*
Variability	Commission errors	Block change SE
Hit reaction time SE	Hit reaction time	Block change
Perseverations	Response style	Change in omissions
Omissions errors		

Table 5: Categorization of Performance Variables

CCPT-II is the latest version of the CCPTs and one of the most popular commercially available CPTs on the market (McGee et al., 2000) and by neuropsychologists the most frequently used CPT (Rabin et al., 2005). Further, repeated testing showed no practice effect and the increased target-to-nontarget ratio in the CCPT-II as opposed to conventional CPTs raises the number of possible correct responses and was therefore hypothesized to increase reliability (Conners 2000) and becomes less susceptible to ceiling and floor effects (Strauss, Sherman & Shren 1998). Internal split-half reliability coefficients were very high for Hit Reaction Time and Omission Errors (r= .95 and .94, respectively), high for Commissions, Standard Error, and d prime (r= .83, .87, and .83, respectively), and in an acceptable range for beta (r= .73) whereas the Variability measure was marginal (r= .66) (Strauss, Sherman & Shren 1998 Conners 2000). Nevertheless, assessment of test-retest stability over the time period of 3 months showed a range from .05 to .92 (Conners 2000) indicating that some variables do not have a good consistency (Homack & Riccio, 2006). However, more than half of the data got acquired from patients with different clinical diagnosis, such as Neurological impaired and ADHD patients and by taking a closer look at the data it becomes clear that the big range is caused by Hit SE Block change and Hit SE ISI change showed which almost seem to show retest performances by chance (.08 and .05, respectively). An earlier version of the CCPT-II (Conners 1992) was evaluated in terms of validity (Epstein et al. 2001) by comparing the performance of ADHD, anxiety disorder patients and controls with two other measures of response inhibition (Posner Visual Orienting Task and a variant of the Stop-Signal task). Commission errors were moderately to highly correlated with the other measure of response inhibition (r= .62 and .43, respectively). Conducting a factor analysis of CCPT and other tests of executive function another study (Barkley et al. 2001) involving a 101 ADHD/ODD patients and normal controls showed that CPT variables emerged on CPT inattention (Omissions, Hit Rate SE, Variability of Hit Rate SE) and CPT inhibition (Commission and Hit rate). Moreover, continuous responding motor demands were suggested to exceed those of other CPTs but performance of CCPT was unrelated to measures of visual processing speed or motor dexterity (McGee et al. 2000). However, a weakness of the test was suggested to be phonological awareness, as imposed by the presentation of alphabetical letters which was shown to be significantly associated with performance in children with reading disorders (McGee et al. 2000). CPTs have generally been reported to be sensitive to drug effects in the treatment of ADHD (Riccio et al. 2001) on one hand but insensitive to socioeconomic status effects on the other (McGee et al. 2000).

A short version of the positive affect negative affect scale (PANAS) was used to see changes in mood and affection (a person´s feelings and emotions) after treadmill running on isocalorifically-matched bouts at three different intensities compared to at rest. The scale consisted of two 10-item questionnaires (see Appendix D). The short version and its two scales has been shown to be reliable, highly internally consistent and stable over a two-months time period (Watson, Clark & Tellegen 1988).

2.3   Study Design and Test Procedures

2.3.1   Exercise Assessment

Subjects were instructed no to perform any physical activity prior to the testing and avoid a physically straining way to get to the laboratory. Time interval between every test was 1 week and testing time of the day was held constant ± 1.5hours. All the running exercise intensity was determined by $\%HR_{max}$. After the baseline value evaluation of CCPT at rest all subjects completed separate sessions on low (LI) and middle intensity (MI) for which the order was randomized, so that they either started with middle intensity running or with low intensity running during which they performed the CCPT. In a second phase of the study, all subjects performed isocalorifically matched exercise bouts, in separate sessions in a randomized order, of LI, MI and high intensity training (HI) (see figure 14).
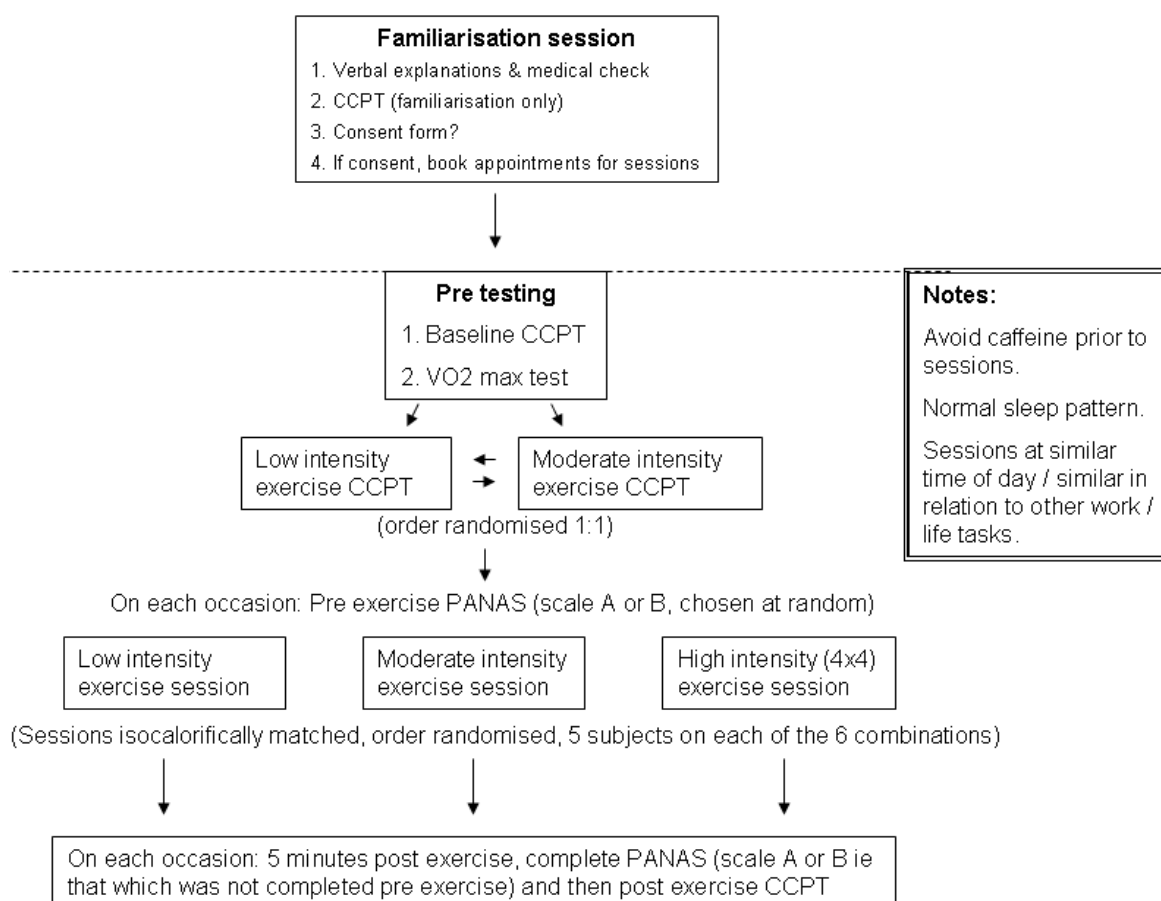
Figure 14: Schematic to show how the data collection phase of the study was carried out
Note. Subjects came to the laboratory at similar times of the day, were instructed about the goal of the study and then signed a consent form. Then a CCPT test at rest was administered and afterwards a VO_{2max} test was carried out. The consequent sessions consisted of CCPT tests during running on either low or moderate intensity, in a randomized order. In a second phase of the study subjects filled out scale A or B of the Positive Affection Negative Affection mood scale before they ran on low, moderate or high intensity consisting of a 4x4 interval session. These sessions were isocalorifically matched and the order of the group was randomized. 5 minutes post treadmill running subjects completed the other part of the mood scale.

For the purposes of the study low intensity exercise was defined as 40% VO_{2max} (~63% HR_{max}), moderate intensity as 60% VO_{2max} (~75 % HR_{max}) and high intensity exercise consisted of 4x4 min interval session at 85% VO_{2max} (~91% HR_{max}) with 40% VO_{2max} (~63% HR_{max}) recovery in between. For the estimation of the relationship between %VO2 and %HR, the American College of Sports Medicine (ACSM) indicates (Swain 1994) that 40, 60 and 85% VO_{2max} can be used as indices for 63, 75 and 91% HR_{max} according to the equation:

$$\% \ HR_{max} = 0.64 * \% \ VO_{2max} + 37 \quad (1).$$

The present study consists of three training intensities. To equate the total amount of work and therefore the energy expenditure in the second phase of the study the equation

$$\%VO_{2max} * VO_{2max} \ (ml * kg * min^{-1}) * BW \ (kg) / 1000 \ = Absolute \ O_2 \ (L * min^{-1}) \quad (2)$$

was used to calculate the absolute oxygen consumption for a given participant by taking into account VO_{2max}, the relative intensity at which work was going to be carried out (%VO_{2max}) and body weight (BW) (McArdle 2009, p. 181-182). %VO_{2max} was different for the three intensities. To total amount of energy expended (TEE) by that participant over a period of time could be estimated by the equation

$$TEE \ (cal) = Absolute \ O_2 \ (L * min^{-1}) * 5kcal * time \ (min) \quad (3)$$

with substituting the Absolute O_2 (L $*$ min^{-1}) value with the one derived from equation (2). The equations (1) – (3) were used to calculate the total amount of energy expenditure in the HI 4x4 Interval session protocol which included a 10min warm-up and a 3min cool-down session at 40% VO_{2max} next to the 16min at 85% VO_{2max} and the 9min at 40% VO_{2max}. The total amount of oxygen and therefore energy used for these 38min of treadmill running was then used to calculate the required time to be spent on the other two intensities. Combining equations (2) and (3) and isolating for time gives the equation

$$Time \ (min) = (TEE * 1000) / (5kcal * \%VO_{2max} \ x \ VO_{2max} \ (ml * kg * min^{-1}) * BW \ (kg)) \quad (4)$$

with which the required amount of time for the LI and MI running could be calculated by substituting equation (4) with the respective %VO_{2max} requirements. This gave a total amount of 56min running on LI and 37.8min running on MI.

All volunteers were randomly allocated to either a group starting with the PANAS mood score letter A or with the letter B (see Appendix D) before every running session in the post phase of the study. After the running session the volunteers had 5 minutes to fill out the PANAS mood score with the respective other letter.

Figure 15: Administration of CCPT during running

2.3.2   Transcranial Direct Current Stimulation

To relate observed exercise effects to frontal cortex activity the transcranial direct current stimulation (tDCS) was used to modulate Frontal cortex excitability. The tDCS by Magstim (neuroConn) applies a weak electrical current to generate an electromagnetic field, which modulates the activity of brain neurons. More particularly, it modifies neuronal transmembrane potentials, thereby influencing the level of excitability and modulating firing rates. Cathodal stimulation over the left DLPFC and a right supraorbital anode was used to reduce whereas anodal stimulation over the left DLPFC and a right supraorbital cathode was used to increase frontal cortex activity. This was done at rest and approximately 5-8min after running exercise. The Saline-soaked electrode (5 cm $\times$ 5 cm) placement of the frontal right supraorbital position was at least 5cm apart from the DLPFC one. To get the left DLPFC position, the skull was measured from the beginning of the nasal bone to the beginning of the skull bone at the back of the head. Together with the measurement from the beginning of both year bones this gave the CF position. From there the left DLPFC was estimated to be 20% of the length from nasal bone to the beginning of the skull bone lateral and anterior (see picture).
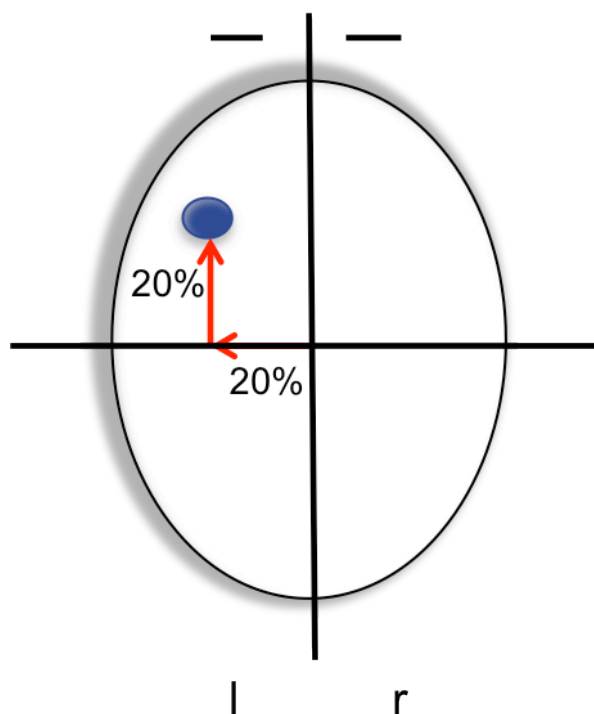
Figure 16: Position of the DLPFC
Note. The figure depicts a model of a scull from above. To assess the location of the dorsolateral prefrontal cortex the skull was measured in length and width from nasal bone to end of skull bone and from ear to ear bone, respectively. The crossing line was marked as the CF position from which the left dorsolateral prefrontal cortex was assumed to be 20% of the skull length laterally and 20% anterior.

Stimulation had a 10sec fade in and fade out phase and was programmed to peak at 2mA. Moreover, total tDCS stimulation had a duration of 900sec and impedance was constantly controlled stay below a value of approximately 6.0. The CCPT test was administered half way through the tDCS stimulation. That is, at rest or after running tDCS was set up for 8min, and then the CCPT test started and the tDCS continued until the half of the CCPT test (7min). This time protocol assured an optimal stimulation of the frontal cortex to see potential differences in the CCPT performance. At this stage of the study four participants were tested for cathodal tDCS at rest. Other pilot data includes anodal tDCS at rest and after running, as well as cathodal tDCS after running. Results of Sham stimulation remain to be seen.

2.3.3 Transcranial Magnetic Stimulation

Repetitive and Continuous transmagnetic stimulation (TMS) with Magstim Rapid[2] (Magstim 200 stimulator, Magstim Co., Dyfed, UK) was used to assess changes in motor evoked potentials (MEP) before and after running exercise and to modulate DLPFC activity with continuous theta burst stimulation (cTBS). At the beginning of each experiment the resting and active motor threshold were assessed for each participant. Resting threshold was defined as the minimum power output of the stimulation that induced reliable MEP (i.e., at least 50 µV amplitude) in at least 5 of 10 consecutive trials when the first dorsal interosseus (FDI) muscle was completely relaxed. Active threshold was

defined as the lowest stimulus intensity at which 5 of 10 consecutive stimuli elicited reliable MEP (i.e., at least 200-300 µV amplitude) in the tonically contracting FDI muscle (ca. 15% of maximal voluntary contraction). Resting and active threshold were evaluated with cTMS even though the mode was switched to cTBS for the conditioning pulses, the intensity of which was set to be below (ca. 80% of) active motor threshold. MEPs were recorded with Ag-AgCl surface electrodes over the right FDI muscle using a belly-tendon montage. The signal was amplified and bandpass filtered (15 to 3500 Hz) by a DIGITIMER D360 amplifier (Digitimer Ltd., Welwyn Garden City, Herts, UK) and recorded at a sampling rate of 5000 Hz for later analysis (SigAvg Software, Cambridge Electronic Design, Cambridge, UK).
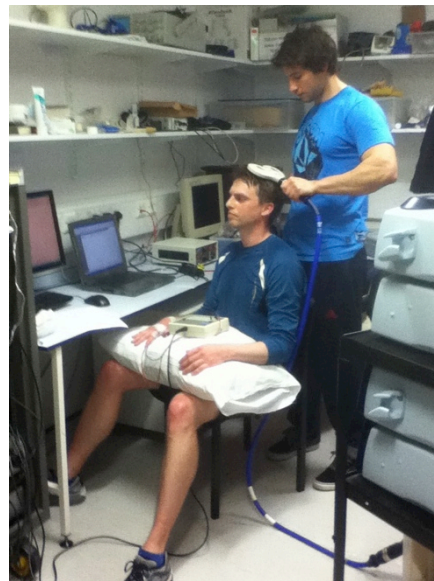
Figure 17: Using continuous theta burst stimulation to modify DLPFC activity post running

The theoretical position of the DLPFC illustrated in the tDCS section was compared to an experimental position, which located the DLPFC 6,5cm anterior and 1cm lateral from the FDI muscle hotspot in the primary motor cortex (M1). The FDI hotspot was the point with the biggest recorded MEP in response to 60-70% power output of single burst stimulations, depending on the individual and typically found 3cm lateral of the CF. Once the appropriate coil positions for rTMS and single-pulse TMS had been arranged, the coil position was marked on a cap covering the head to ensure an accurate repositioning of the coil after the running exercise. The stimulation coil was held by hand, and coil position was continuously monitored throughout the experiment. The time protocol for cTBS stimulation over the left DLPFC was 40sec, 50Hz and 5Hz trains to induce LTD. The coil was held tangentially to the skull with the handle pointing 45° postero-laterally. The intensity of cTBS was referenced to the individual active motor threshold when the same coil was placed over the "hot spot" of the motor hand area. This intensity was set to 80% active threshold. At this stage of the study only pilot data is available for cTBS of the DLPFC at rest and after running.

2.4   Statistical Analysis

Statistical analysis was performed using the software program SPSS 19.0. With at least 14 and 13 participant in each group statistical power of at least $\beta > .08$ was given for all the analysis. Due to a high number of subjects, normal distribution of the dependent variables was assumed, which was confirmed by histograms and therefore parametric tests could be adopted. To evaluate overall differences in CCPT performance variables within-subjects repeated measures Analysis of Variance (ANOVA) were carried out because the means of the variables measured (with CCPT) were dependent on the different testing conditions and comparisons were made within the same subjects in the different conditions (intensity). Therefore, each measurement represented testing of the same characteristics under different conditions, which means that intensity effects are compared across multiple measures in the same subjects. If equality of both, the variances of the differences between the repeated measures, and the correlation among the repeated measures were not given (sphericity) in the Mauchly´s test of Sphericity, the Greenhouse-Geissner correction (1959) was applied unless epsilon was >.75 because in that condition Huynh & Feldt (1976) reported that too many false null hypothesis failed to be rejected which was also shown to be true with sphericity (G-G epsilon) estimates as high as .9 (Collier, Baker, Mandeville & Hayes 1967). Therefore, the Huynh & Feldt correction was used instead for (GG)e>0.75 and the Greenhouse Geissner correction for e<0.75 (Girden 1992). However, the Huynh & Feldt correction (epsilon strich) was shown (Maxwell & Delaney 1990) to slightly overestimate sphericity. A GGepsilon value closer to 1/(k-1) than to 1, where k is the number of levels of the independent variable (intensity) was considered a substantial deviation from the sphericity assumption. Polynomial contrast analyses gave trends (quadratic and linear) and Bonferroni-adjusted post-hoc analyses were used to see contrasts and the direction of the differences because the independent variable (intensity) had a meaningful order and the Bonferroni method was concluded (Fields 2005, p. 441-444) to be the most robust of the univariate techniques, especially in terms of power and control of the type I error rate when the sphericity assumption is violated. For the significant results also independent t-tests with Age, Gender and VO_{2max} as grouping variables were conducted to see differences in baseline values. The assumption of equality of variances was calculated by Leven´s test. Repeated measures ANOVA with between-subjects factor/interaction effects for which heterogeneity was indicated (two groups high/low were independent from each other) were carried out to see if the dependent variables VO_{2max}, Age and Gender had an effect on the exercise induced changes in CCPT performance. For analyses of single block values and mood differences in the post running phase the paired-sample T-test was used to detect differences in either the positive or negative affection scale because similarly to the repeated measure ANOVA the same subjects were compared in different conditions. Normality was given as indicated as indicated before and the assumption of equality of variances was calculated by Leven´s test. Correlations were done with Pearson´s correlation coefficient. Within-subjects repeated measure ANOVA were also used to detect differences in reaction time and commission error in different ISI

presentations. All values are expressed as mean ± standard deviation (SD). A two-tailed $P < 0.05$ was accepted as statistically significant for all statistical tests.

3   Results

3.1   Results During

3.1.1   CCPT Performance Variables

Reaction Time

A one-way within subjects (or repeated measures) ANOVA was conducted to compare the effect of exercise intensity on reaction time. Reaction times were 309.15 ± 39.42ms, 323.24 ± 34.11ms and 324.07 ± 34.44ms for resting, low and moderate intensity, respectively. Mauchly´s test indicated that the assumption of sphericity had not been violated ($\chi^2(2) = 3.27$, $p > 0.05$); therefore degrees of freedom were not corrected. The overall results from the one-way repeated measures (within subjects) ANOVA showed that reaction time was significantly affected by Exercise Intensity $F(2, 58) = 7.48$, $p < 0.005$, $\eta p2 = 0.21$. Observed power was .93. Polynomial trend analyses showed a significantly linear fashion of increase in reaction time with exercise intensity $F(1,29) = 9.10$, $p < 0.05$, $\eta p2 = 0.24$ with a power of .83. Bonferroni adjusted post-hoc analyses indicated that reaction time during moderate intensity was significantly different from baseline ($p < 0.05$) but not from low intensity ($p > 0.05$). Moreover, reaction time during low intensity was significantly different from baseline ($p < 0.05$). These results suggest that exercise intensity really does have an effect on reaction time. Specifically, the results suggest that reaction time increases with exercise intensity. However, there is no real difference in reaction time when comparing low and moderate exercise intensity.

Figure 18: Reaction Time during running
Note. The x-axis represents the 3 conditions, baseline, low intensity and moderate intensity. On the y-axis reaction time is measured in milliseconds. The overall repeated-measures ANOVA was significant and Bonferroni adjusted post-hoc measures indicated that reaction time at baseline was different from reaction time at low and moderate intensity.

Commission Errors

A one-way within subjects (or repeated measures) ANOVA was conducted to compare the effect of exercise intensity on commission errors. Commission errors were 17.47 ± 7.38, 18.03 ± 8.89 and 19.93 ± 8.82 for resting, low and moderate intensity, respectively. Mauchly´s test indicated that the assumption of sphericity had not been violated ($\chi^2(2) = 2.63$, $p > 0.05$); therefore degrees of freedom were not corrected. The polynomial trend analyses showed a significantly linear fashion of increase in commission errors with exercise intensity $F(1,29) = 4.23$, $p < 0.05$, $\eta p2 = 0.13$ with a power of .51. However, the overall results from the one-way repeated measures (within subjects) ANOVA showed that commission errors were not significantly different during different exercise intensities $F(2, 58) = 3.02$, $p = 0.057$, $\eta p2 = 0.09$. Observed power was .56. Bonferroni adjusted post-hoc analyses confirmed this by indicating that there was no significant difference between the commission errors made at baseline and during low intensity ($p > 0.05$), as well as during moderate intensity ($p > 0.05$). These results suggest that there is a strong tendency that exercise intensity has an effect on inhibitory/executive control. Specifically, the results suggest that commission errors increase with

exercise intensity in a linear, intensity dependent fashion. However, the fact that the overall result of the used statistical model is only close to significance is likely due to low observed power.

Figure 19: Commission Errors during running
Note. The x-axis represents the 3 conditions, baseline, low intensity and moderate intensity. On the y-axis the amount of commission errors is presented. The overall repeated-measures ANOVA was close to significance.

Reaction Time Standard Error

A one-way within subjects (or repeated measures) ANOVA was conducted to compare the effect of exercise intensity on reaction time standard error. Reaction time standard errors were 4.19 ± 1.21, 3.64 ± 0.97 and 3.74 ± 1.05 for resting, low and moderate intensity, respectively. Mauchly´s test indicated that the assumption of sphericity had not been violated ($\chi^2(2) = 2.71$, $p > 0.05$); therefore degrees of freedom were not corrected. The overall results from the one-way repeated measures (within subjects) ANOVA showed that there was a significant effect of exercise intensity on reaction time standard error $F(2, 58) = 3.96$, $p < 0.05$, $\eta p2 = 0.12$. Observed power was .69. Polynomial trend analyses showed a significantly quadratic fashion of change in reaction time standard error with exercise intensity $F(1,29) = 4.54$, $p < 0.05$, $\eta p2 = 0.14$ with a power of .54. Bonferroni adjusted post-hoc analyses indicated that reaction time standard error during moderate intensity was not significantly different from reaction time standard error at baseline ($p > 0.05$) and from the low intensity condition ($p > 0.05$). Instead, reaction time standard error during low intensity was significantly different from baseline ($p < 0.05$). These results suggest that exercise intensity really does have an effect on the consistency of reaction times throughout the test. Specifically, the results suggest that reaction time

standard error was lowest during low intensity running. However, there is no difference in reaction time standard error when comparing low and moderate exercise intensity.
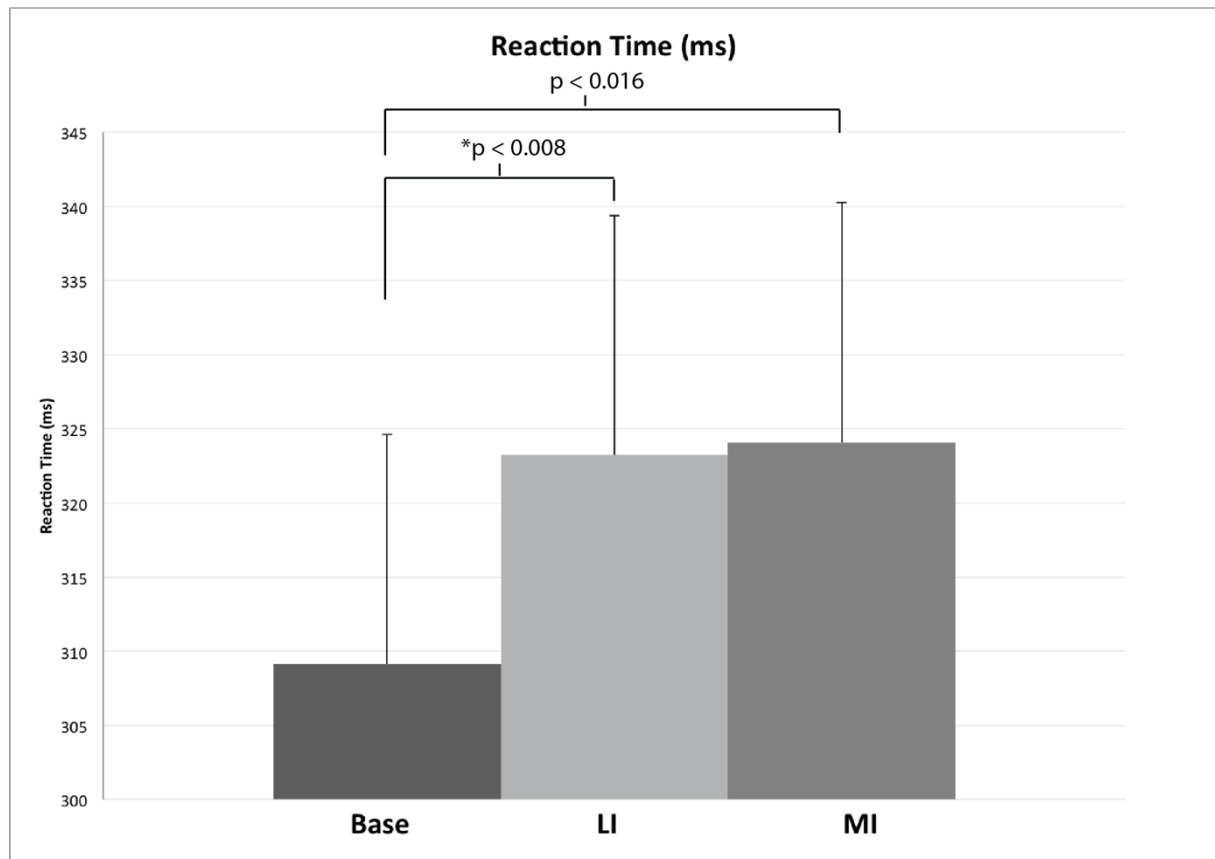

Figure 20: Reaction Time Standard Error during running
Note. The x-axis represents the 3 conditions, baseline, low intensity and moderate intensity. On the y-axis reaction time standard error is depicted. The overall repeated-measures ANOVA was significant and Bonferroni adjusted post-hoc measures indicated that reaction time standard error at baseline was different from reaction time standard error at low intensity.

Reaction Time ISI change

A one-way within subjects (or repeated measures) ANOVA was conducted to compare the effect of exercise intensity on reaction time ISI change. Reaction time ISI change was 0.035 ± 0.023, 0.043 ± 0.023 and 0.044 ± 0.020 for resting, low and moderate intensity, respectively. Mauchly´s test indicated that the assumption of sphericity had not been violated ($\chi^2(2) = 3.07$, $p > 0.05$); therefore degrees of freedom were not corrected. The overall results from the repeated measures ANOVA showed that reaction time interstimulus interval change was significantly affected by Exercise Intensity $F(2, 58) = 3.21$, $p < 0.05$, $\eta p2 = 0.10$. Observed power was .59. Polynomial trend analyses showed a significantly linear increase in reaction time ISI change with exercise intensity $F(1,29) = 4.87$, $p < 0.05$, $\eta p2 = 0.14$ with a power of .57. Bonferroni adjusted post-hoc analyses indicated no significant change in reaction time ISI change in any of the exercise intensity conditions ($p > 0.05$). These results suggest that exercise intensity really does have an effect on the change of reaction time at different ISIs. Specifically, the results suggest that adjustment to the different ISIs got worse with

intensity (longer reaction times with increasing ISIs). However, there is no difference in reaction time ISI change when comparing low and moderate exercise intensity.

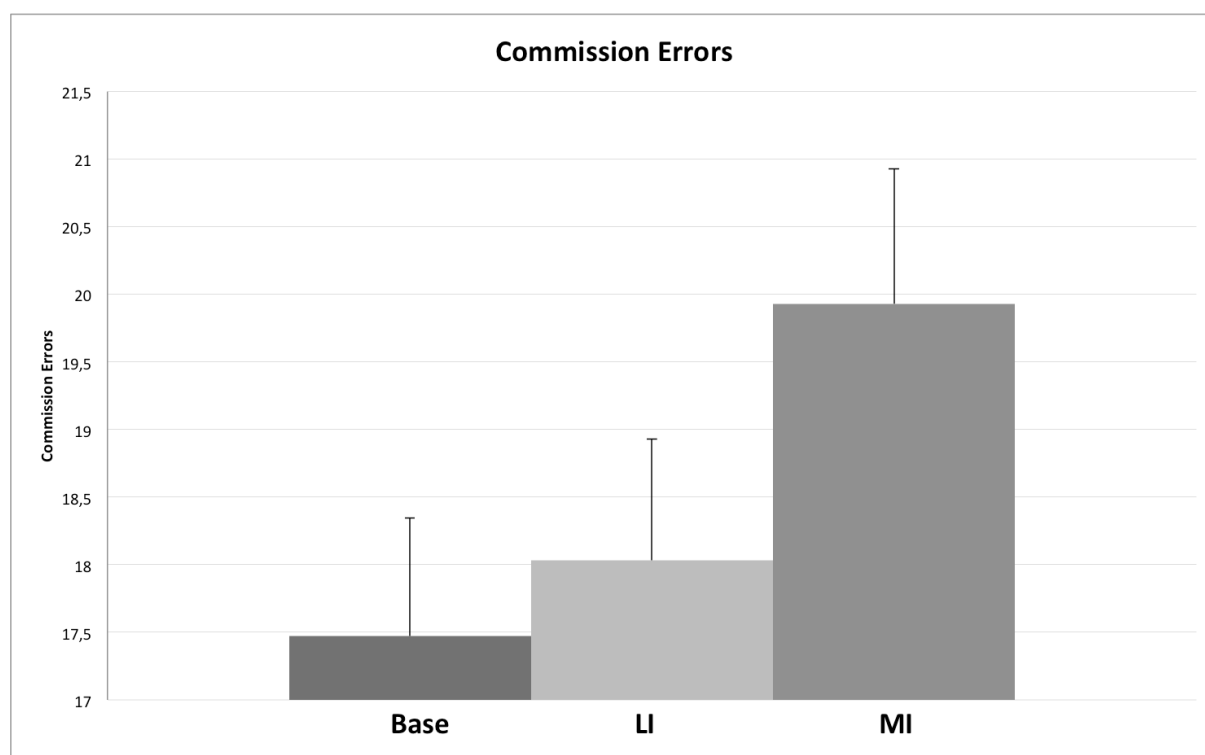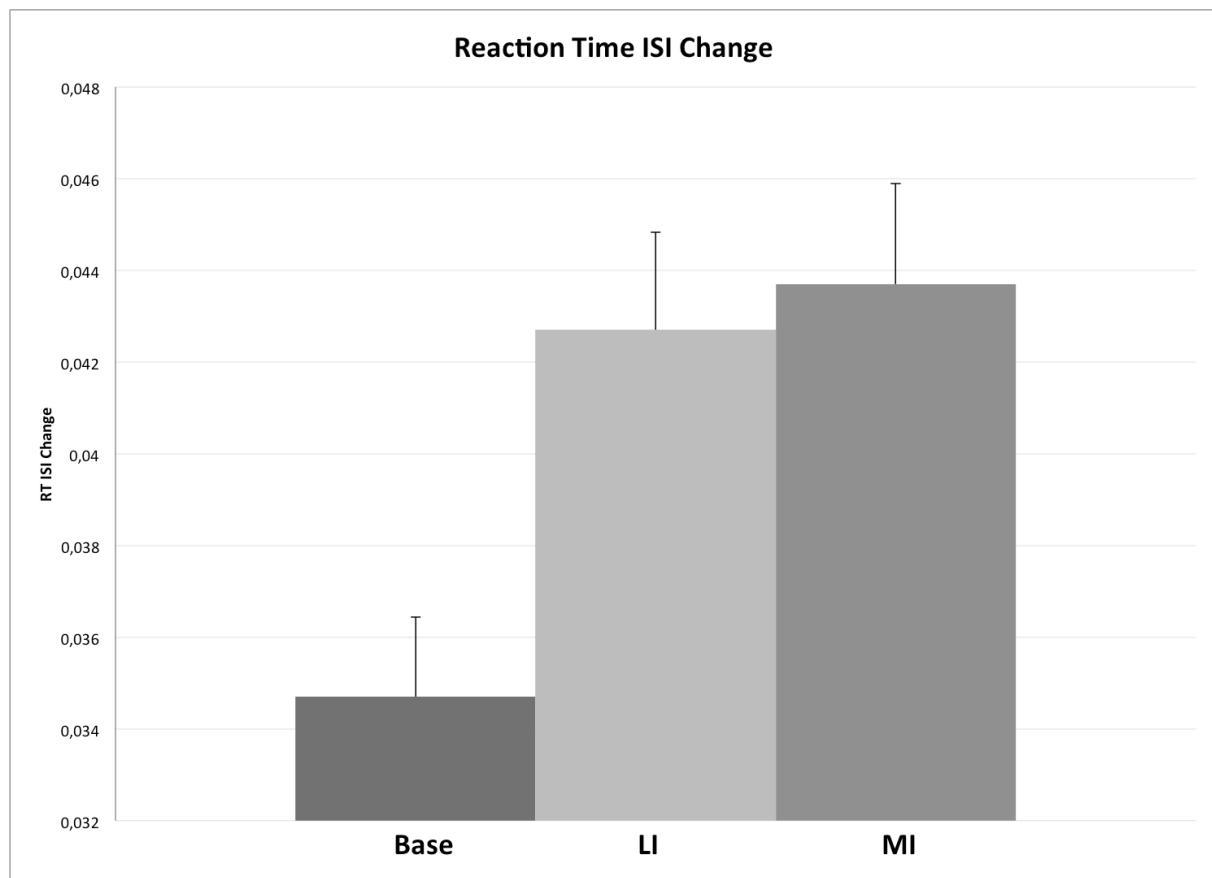**Figure 21: Reaction Time ISI change during running**
Note. The x-axis represents the 3 conditions, baseline, low intensity and moderate intensity. On the y-axis reaction time interstimuli interval change is shown. The overall repeated-measures ANOVA was significant but Bonferroni adjusted post-hoc measures indicated no particular differences.

3.1.2   Single Block Analysis

Analyses of single block Reaction Time and Commission Error with different ISI

Paired samples t-tests were conducted to detect in-depth changes in reaction time and commission errors from the first three blocks (1,2 and 3) to the last three blocks (16, 17 and 18) in the resting position, during low and during moderate intensity running. By doing that, the 1st and the 17th, the 2nd and the 18th and the 3rd and the 16th block were compared because they had 1, 2 and 4 second ISI, respectively.

Reaction Time in Block 1 compared to Block 17 (1sec ISI)

Reaction time during the 1 sec ISI was shown to change significantly from block 1 (311.6 ± 39.32ms) to block 17 (298.3 ± 37.13ms) during the **low intensity** condition; $t(29) = 2.737$, $p < 0.05$. There were no significant differences in reaction time in the 1sec ISI from block 1 to block 17 in the resting

condition (289.33 ± 42.59ms and 284.1 ± 45.98ms); t(29)=0.709, p > 0.05 or during the moderate intensity running (299.37 ± 43.45ms and 297.23 ± 39.33ms, respectively); t(29)=0.474, p > 0.05. These results suggest that during the time period of the test (14min) low intensity but not resting or moderate intensity has an effect on reaction time when the visual stimuli are presented with a 1sec ISI. Specifically, the results suggest that reaction time decreases within a bout of 14min running on low intensity. However, in the resting condition and during moderate intensity there is no difference in reaction time during the 14min duration of the CCPT test.

Commission Error in Block 1 compared to Block 17 (1sec ISI)

Commission Errors during the 1 sec ISI showed no significantly change from block 1 to block 17 in any condition (all p´s > 0.05). The baseline commission error went in block 1 from 1.17 ± 0.65 to 0.87 ± 0.68; t(29)=1.964, p > 0.05 the low intensity ones from 0.87 ± 0.78 to 1.07 ± 0.69; t(29)=-1.235, p > 0.05 and the commission error made during moderate intensity changed from 1.13 ± 0.82 to 1.07 ± 0.74; t(29)=0.372, p > 0.05. These results suggest that during the time period of the test (14min) none of the exercise intensities had an effect on commission errors when the visual stimuli are presented with a 1sec ISI.

Reaction Time in Block 2 compared to Block 18 (2sec ISI)

Reaction time during the 2 sec ISI was shown to change significantly from block 2 to block 18 during the **low intensity** condition (328.37 ± 41.53ms to 318.23 ± 34.03ms); t(29)=2.155, p < 0.05 as well as during the **moderate intensity** condition (312.47 ± 27.48ms to 323.13 ± 35.17ms); t(29)=-2.412, p < 0.05. There was no significant difference in reaction time in the 2sec ISI from block 2 (288.50 ± 34.95ms) to block 18 (295.43 ± 40.54ms) in the resting condition; t(29)=-1.157, p > 0.05. These results suggest that during the time period of the test (14min) low intensity and moderate intensity but not the resting condition had an effect on reaction time when the visual stimuli are presented with a 2sec ISI. Specifically, the results suggest that reaction time decreases within a bout of 14min running on low intensity whereas reaction time increases within 14min running on moderate intensity. However, in the resting condition there is no difference in reaction time during the 14min duration of the CCPT test.

Commission Error in Block 2 compared to Block 18 (2sec ISI)

Commission Error during the 2 sec ISI was shown to change significantly from block 2 to block 18 during the **low intensity** condition (1.37 ± 0.76 to 1.00 ± 0.69); t(29)=2.626, p < 0.05 as well as during the **moderate intensity** condition (0.97 ± 0.72 to 1.4 ± 0.67); t(29)=-2.765, p < 0.05. There was no significant difference in commission error in the 2sec ISI from block 2 (1.13 ± 0.63) to block 18 (0.83 ± 0.79) in the resting condition; t(29)=1.663, p > 0.05. These results suggest that during the time period of the test (14min) low intensity and moderate intensity but not the resting condition had an effect on commission error when the visual stimuli are presented with a 2sec ISI. Specifically, the results suggest that commission error decreases within a bout of 14min running on low intensity whereas commission error increases within 14min running on moderate intensity. However, in the

resting condition there is no difference in commission error during the 14min duration of the CCPT test.

Reaction Time in Block 3 compared to Block 16 (4sec ISI)

Reaction time during the 4 sec ISI showed no significantly change from block 3 to block 16 in any of the conditions (all p´s > 0.05). Reaction time during baseline went from 317.57 ± 45.20ms to 325.83 ± 46.11ms; $t(29)=-1.721$, $p > 0.05$ during low intensity from 340.50 ± 45.81ms to 344.37 ± 38.20ms; $t(29)=-0.612$, $p > 0.05$ and during moderate intensity from 338.53 ± 39.51ms to 350.33 ± 39.61ms; $t(29)=-2.027$, $p > 0.05$. These results suggest that during the time period of the test (14min) none of the exercise intensities had an effect on reaction time when the visual stimuli are presented with a 4sec ISI. However, reaction time during 4sec ISI showed a trend (338.53 ± 39.51ms to 350.33 ± 39.61ms; $t(29)=-2.027$, $p = 0.52$) to increase within 14min running on moderate intensity.

Commission Error in Block 3 compared to Block 16 (4sec ISI)

Commission Error during the 4 sec ISI was shown to change significantly from block 3 (0.87 ± 0.57) to block 16 (1.23 ± 0.73) during the **moderate intensity** condition; $t(29) = -2.257$, $p < 0.05$. There were no significant differences in commission error in the 4sec ISI from block 3 to block 16 in the resting condition (1.03 ± 0.85 and 0.97 ± 0.76); $t(29)=0.372$, $p > 0.05$ or during the low intensity running (1.13 ± 0.73 and 0.83 ± 0.75); $t(29)=1.874$, $p > 0.05$. These results suggest that during the time period of the test (14min) moderate intensity but not resting or the low intensity condition has an effect on reaction time when the visual stimuli are presented with a 4sec ISI. Specifically, the results suggest that reaction time increases within a bout of 14min running on moderate intensity. However, during low intensity a trend for a decrease in commission errors was evident ($p = 0.71$) and in the resting condition there was no difference in commission error during the 14min duration of the CCPT test.
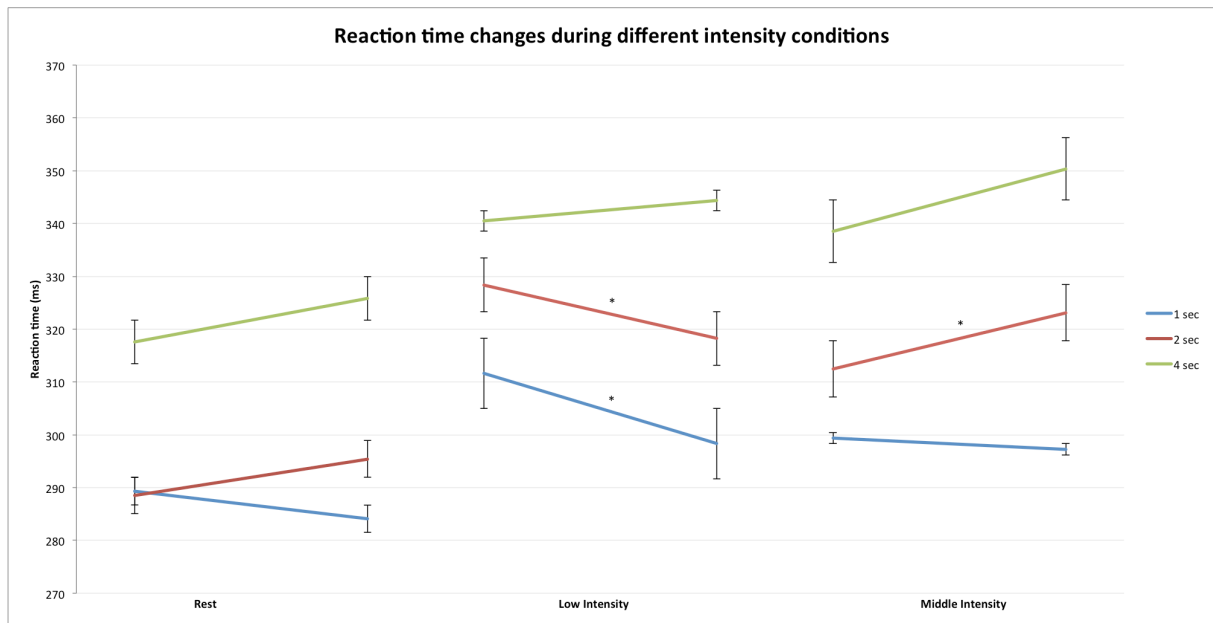
Figure 22: Reaction Time changes during running
Note. The x-axis represents the course during the 3 conditions baseline, low intensity and moderate intensity. On the y-axis reaction time is measured in milliseconds. The blue line indicates the 1 second interstimuli interval presentation, the red line the 2 seconds interstimuli interval period, the green line the 4 seconds interstimuli interval presentation. Paired-sample t-tests showed that during low intensity running reaction time decreased in both, the 2 and 4 seconds interstimuli interval presentations. During moderate intensity reaction time increased in the 2 second interstimuli interval condition during the time course of the test. Significance level was measured at the $p < 0.05$ level.
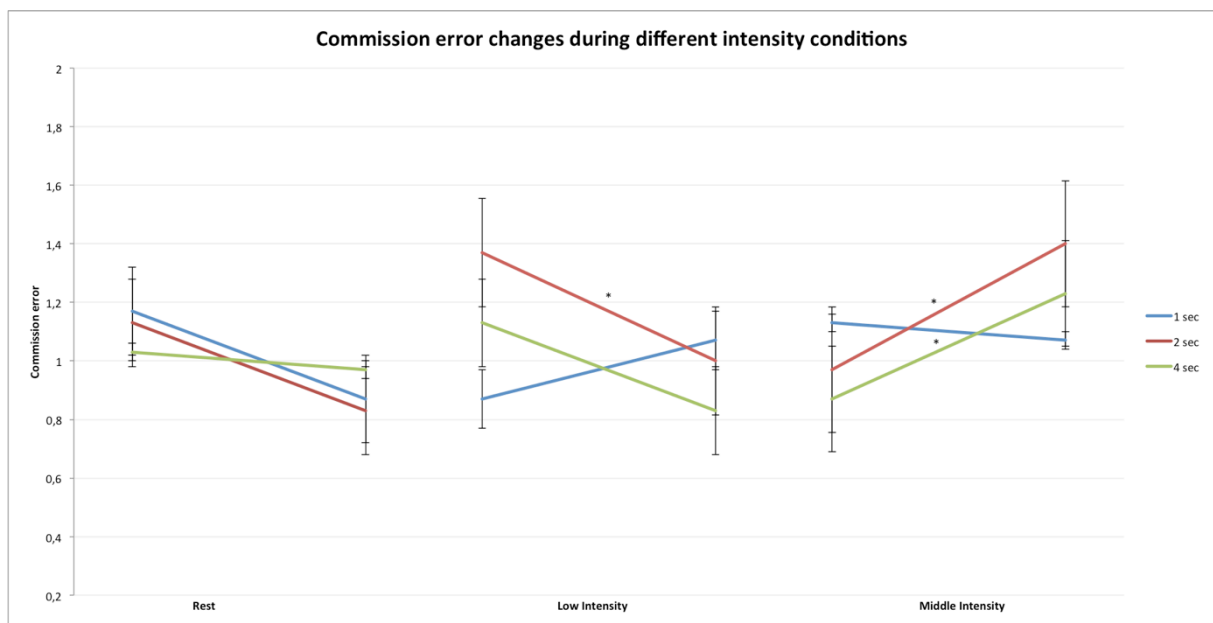
Figure 23: Commission Error changes during running
Note. The x-axis represents the course during the 3 conditions baseline, low intensity and moderate intensity. On the y-axis the amount of commission errors is depicted. The blue line indicates the 1 second interstimuli interval presentation, the red line the 2 seconds interstimuli interval period, the green line the 4 seconds interstimuli interval presentation. Paired-sample t-tests showed that during low intensity running commission errors decreased in the 2 seconds interstimuli interval presentation. During moderate intensity reaction time increased in both, the 2 and 4 second interstimuli interval conditions during the time course of the test. Significance level was measured at the $p < 0.05$ level.

3.1.3   Interstimuli Interval comparison

Comparing Reaction Time and Commission Error in different ISI (1,2 and 4sec)

Repeated measures (within-subjects) ANOVA was conducted to detect differences in reaction time and commission errors when participants were presented with 1, 2 and 4sec ISIs. To do that, the 1, 2 and 4sec ISI, which were presented in block 1, 2 and 3, respectively, and block 17, 18 and 16, respectively were analysed for changes in reaction time and commission errors in the baseline, as well as during low and during moderate exercise intensity. In all 6 conditions it could be shown (all p´s < 0.005) that **reaction time** increased with ISI in a linear trend fashion (all p´s < 0.005) and Bonferroni corrected post-hoc analyses showed that in all analyses at least reaction time for the 4sec ISI was significantly different from the 2sec and 1sec ISI (all p´s < 0.05).
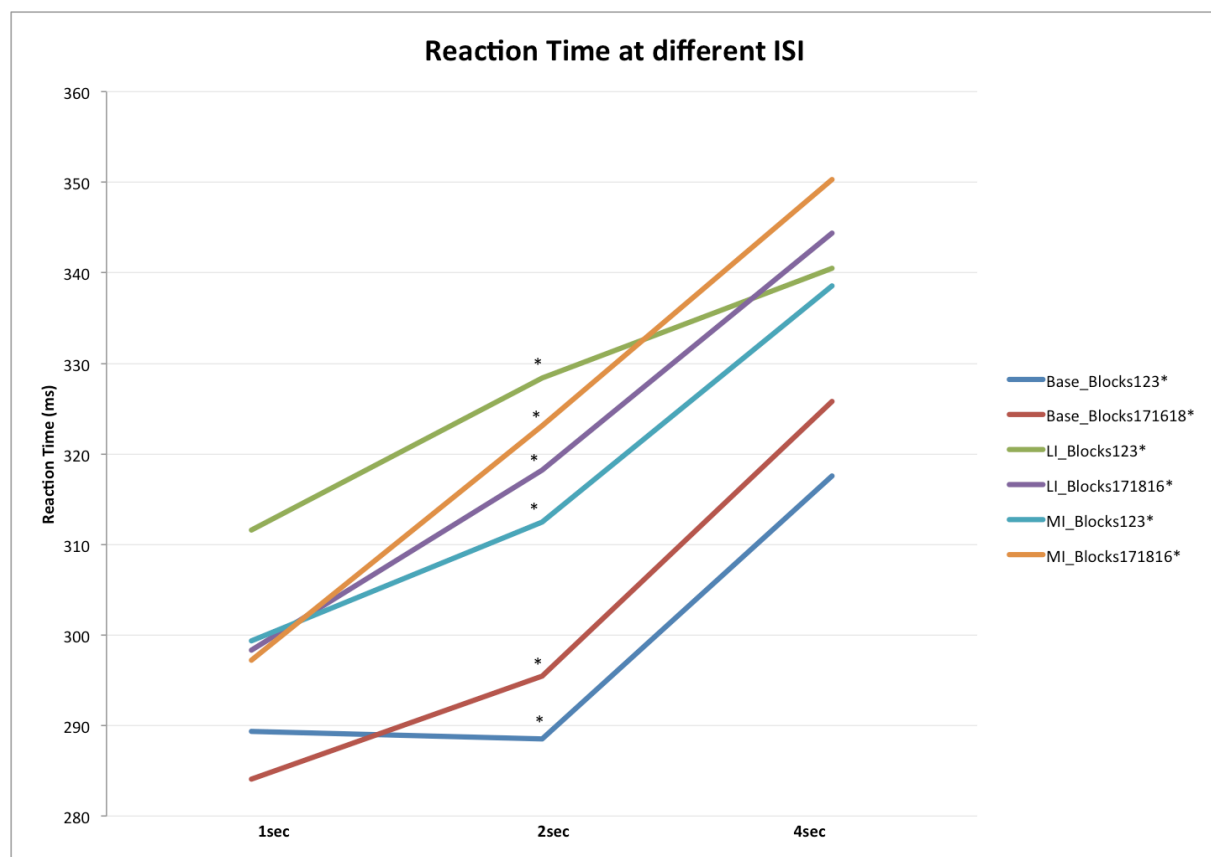
Figure 24: Reaction Time during 1, 2 and 4 second ISI
Note. The x-axis represents the 1, 2 and 4 seconds interstimuli intervals. The y-axis shows the reaction time measured in milliseconds. The blue, green and turquoise lines indicate reaction times at the beginning of the test, measured from the first three blocks during rest, low and moderate intensity, respectively. The red, purple and orange line indicate reaction times at the end of the test measured in the last three blocks during rest, low and moderate intensity, respectively. All conditions were significant as indicated by *. Error bars have been removed for clarity.

Commission errors, however, were only significantly different in the 1 (0.87 ± 0.78), 2 (1.37 ± 0.76) and 4sec (1.13 ± 0.73) ISI conditions during low intensity exercise, at the beginning of the CCPT test (blocks 1, 2 and 3) $F(2, 58) = 4.047$, $p < 0.05$, $ηp2 = 0.12$. Observed power was .70. Polynomial trend analyses showed a significant quadratic trend $F(1, 29) = 5.579$, $p < 0.05$, $ηp2 = 0.16$ with an observed power of .63. Bonferroni adjusted post-hoc analyses indicated that the commission errors during the 1sec ISI was significantly ($p < 0.05$) different from the 2sec ISI presentation.
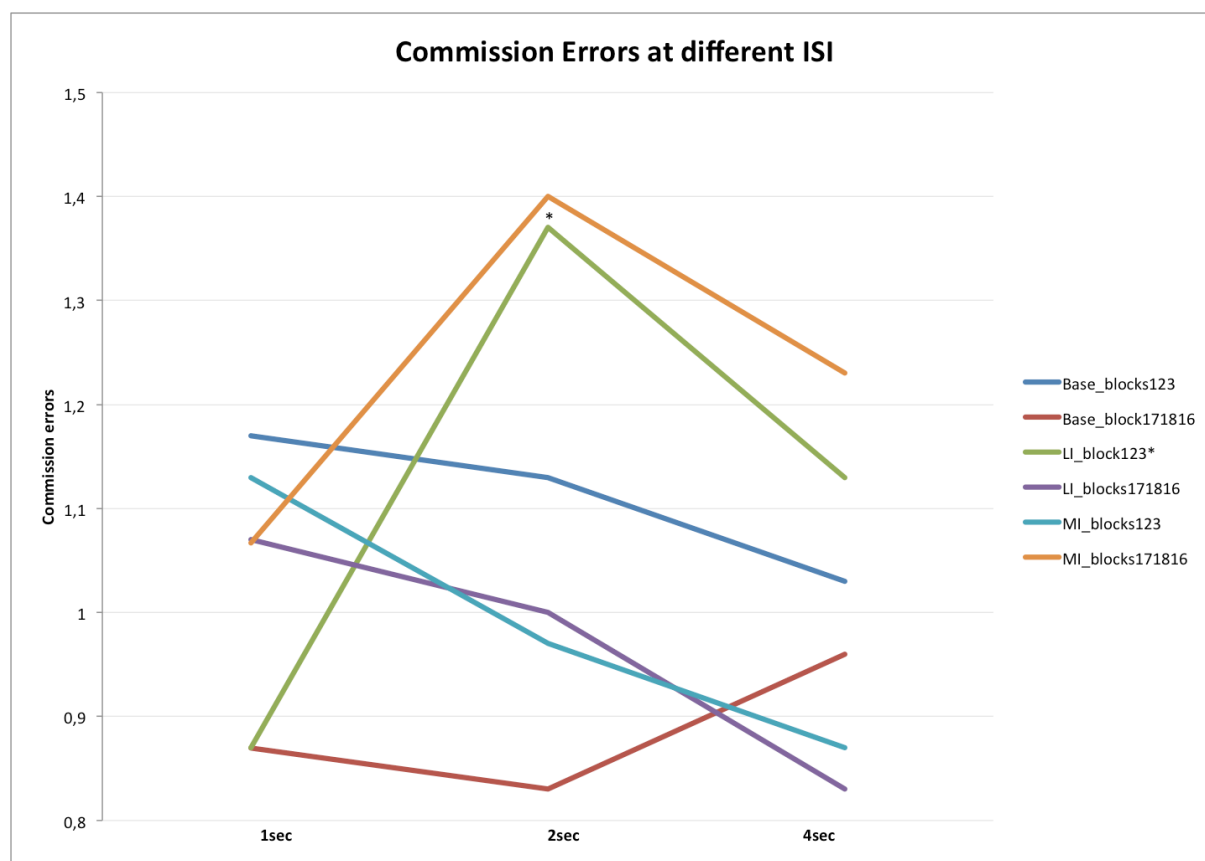
Figure 25: Commission Error during 1, 2 and 4 second ISI
Note. The x-axis represents the 1, 2 and 4 seconds interstimuli intervals. The y-axis shows the amount of commission errors. The blue, green and turquoise lines indicate commission errors at the beginning of the test, measured from the first three blocks during rest, low and moderate intensity, respectively. The red, purple and orange line indicate commission errors at the end of the test measured in the last three blocks during rest, low and moderate intensity, respectively. Only the first three blocks during low intensity running was significant different as indicated by *. Error bars have been removed for clarity.

These results suggest that during all running intensities and rest reaction time for the different ISI was different. Commission errors during block 1, 2 and 3 of the CCPT test on low intensity running were also different in the different ISI presentations. Specifically these results suggest that reaction time increased linearly with the length of the ISI and was therefore always highest for the 4sec ISI presentation. Moreover, inhibitory control, as measured by commission errors at the beginning of low intensity running was most impaired in the 2sec ISI presentation. Even though not significant, commission errors made during 1, 2 and 4sec ISIs in the last three blocks (16, 17 and 18) of moderate

intensity running showed a tendency (p = 0.53) to differ from each other in a similar way as during the first three block of low intensity exercise.

3.2   Results Post

3.2.1   CCPT Performance Variables

Reaction Time

A one-way within subjects (or repeated measures) ANOVA was conducted to compare the effect of exercise intensity on reaction time post exercise. Reaction times were 311.17 ± 38.46ms, 284.31 ± 34.54ms, 279.66 ± 31.92ms and 275.23 ± 29.36ms for resting, low, moderate and high intensity, respectively. Mauchly´s test indicated that the assumption of sphericity had been violated ($\chi^2(5) =$ 24.40, p < 0.05); since the Greenhouse-Geissner estimate of sphericity (ε = .6) was closer to 1/(k - 1) than to 1, where k is the levels of conditions, degrees of freedom were corrected according the Huynh & Feldt estimate of sphericity ($\varepsilon´$ = .64). The overall results from the one-way repeated measures (within subjects) ANOVA showed that reaction time after running was significantly affected by Exercise Intensity F(1.91, 49.72) = 24.06, p < 0.005, ηp2 = 0.48. Observed power was 1.00. Polynomial trend analyses showed a significantly linear fashion of decrease in reaction time with exercise intensity F(1,26) = 42.66, p < 0.005, ηp2 = 0.62 with a power of 1.00. Bonferroni corrected pairwise comparisons indicated that reaction time in all three post conditions was significantly different from baseline values (p < 0.005). Moreover, reaction time after high intensity was also shown to be significantly different from the reaction time after low intensity running (p < 0.05). These results suggest that exercise intensity really does have an effect on reaction time after exercise. Specifically, the results suggest that reaction time decreases with exercise intensity in a linear, intensity dependent fashion.

Figure 26: Reaction Time post running
Note. The x-axis represents the 4 conditions, baseline, low intensity, moderate intensity and high intensity post running. On the y-axis reaction time is measured in milliseconds. The overall repeated-measures ANOVA was significant implying a linear decrease in reaction time with intensity and Bonferroni adjusted post-hoc measures indicated that reaction time at baseline was different from reaction time after low, moderate and high intensity. Moreover, low intensity was different from high intensity.

Commission Errors

A one-way within subjects (or repeated measures) ANOVA was conducted to compare the effect of exercise intensity on commission errors. Commission errors were 17.26 ± 6.78, 19.07 ± 7.90, 20.37 ± 7.99 and 19.00 ± 8.33 for resting, low, moderate and high intensity, respectively. Mauchly´s test indicated that the assumption of sphericity had not been violated ($\chi^2(5) = 10.67$, $p > 0.05$); therefore degrees of freedom were not corrected. The polynomial trend analyses showed a significant quadratic trend in the change of the commission errors $F(1, 26) = 68.48$, $p < 0.05$, ηp2 $= 0.16$ with a power of .56. However, the overall results from the one-way repeated measures (within subjects) ANOVA showed that commission errors were not significantly different after different exercise intensities $F(3, 78) = 2.68$, $p > 0.05$, ηp2 $= 0.09$. Observed power was .63. Bonferroni corrected post-hoc analyses confirmed this by indicating that there were no significant differences between any conditions ($p > 0.05$). These results suggest that there is a strong tendency that exercise intensity has an effect on inhibitory/executive control after running. Specifically, the results suggest that commission errors have a tendency to increase with exercise intensity in a linear, intensity dependent fashion. However,

the fact that the overall result of the used statistical model is only close to significance is likely due to low observed power.

Figure 27: Commission Error post running
Note. The x-axis represents the 4 conditions, baseline, low intensity, moderate intensity and high intensity post running. On the y-axis the amount of commission errors is shown. The overall repeated-measures ANOVA was close to significance.

Response Style

A one-way within subjects (or repeated measures) ANOVA was conducted to compare the effect of exercise intensity on response style. Response style values were 0.44 ± 0.40, 0.28 ± 0.22, 0.48 ± 0.38 and 0.29 ± 0.30 for resting, low, moderate and high intensity, respectively. Mauchly´s test indicated that the assumption of sphericity had been violated ($\chi^2(5) = 17.92$, $p < 0.05$); since the Greenhouse-Geissner estimate of sphericity ($\varepsilon = .66$) was as close to $1/(k - 1)$ as to 1, where k is the levels of conditions, the mean of the p-value for both, the Greenhouse-Geissner ($\varepsilon = .66$), and the Huynh & Feldt ($\varepsilon´ = .71$) estimates of sphericity to correct the degrees of freedom were taken into consideration. The overall results from the one-way repeated measures (within subjects) ANOVA showed that exercise intensity had a significantly effect on response style $F(2.06, 53.50) = 3.63$, $p < 0.05$, ηp2 = 0.12. Observed power was .65. Polynomial trend analyses showed a cubic trend $F(1,26) = 18.42$, $p < 0.005$, ηp2 = 0.42 with a power of .99. Bonferroni corrected pairwise comparisons indicated that response style was different after low and moderate intensity exercise ($p < 0.05$) and after moderate and high intensity ($p < 0.05$). These results suggest that exercise intensity has an effect on the construct of risky versus cautious behavior. Specifically, the results suggest that low and high intensity

led to a rather risky response style compared to the rather cautious response style after moderate intensity running.
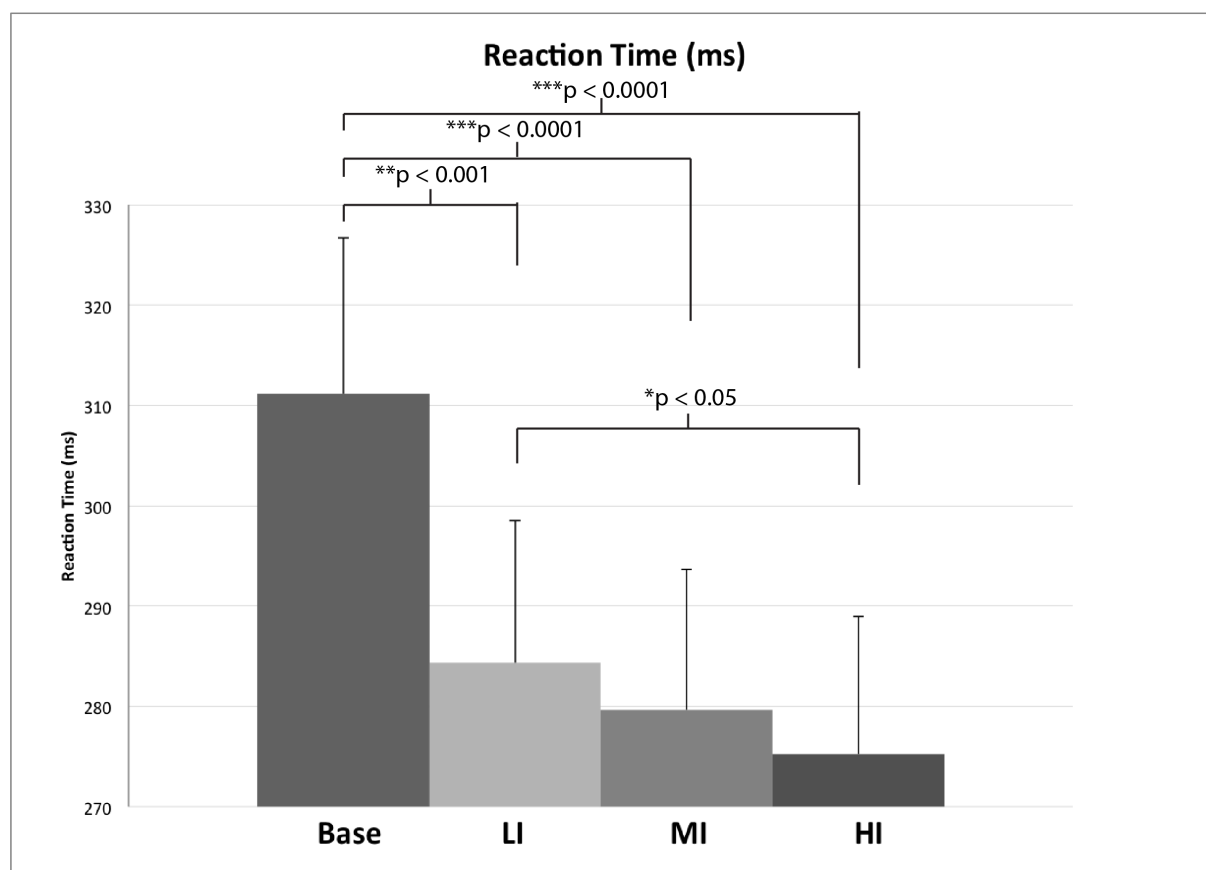

Figure 28: Response Style post running
Note. The x-axis represents the 4 conditions, baseline, low intensity, moderate intensity and high intensity post running. On the y-axis a measure of response style is shown. The overall repeated-measures ANOVA was significant and Bonferroni adjusted post-hoc measures indicated that response style after low intensity running was different from the values after moderate intensity running. Moreover, response style after moderate intensity was different from the response style observed after high intensity running.

Perseverations

A one-way within subjects (or repeated measures) ANOVA was conducted to compare the effect of exercise intensity on perseveration errors. Perseveration errors were 0.48 ± 1.09, 2.04 ± 2.90, 2.33 ± 4.16 and 2.00 ± 2.75 for resting, low, moderate and high intensity, respectively. Mauchly´s test indicated that the assumption of sphericity had not been violated ($\chi^2(5) = 10.23$, $p > 0.05$); therefore degrees of freedom were not corrected. The overall result from the one-way repeated measures (within subjects) ANOVA showed that perseveration errors were significantly affected by exercise intensity $F(3, 78) = 3.20$, $p < 0.05$, $\eta p2 = 0.11$. Observed power was .72. Polynomial trend analyses showed a significant linear fashion in the change of perseveration errors with increasing exercise intensity $F(1,26) = 5.53$, $p < 0.05$, $\eta p2 = 0.18$ with a power of .62. Bonferroni adjusted, pairwise comparisons indicated that perseveration errors in none of the three post conditions were significantly different from either baseline ($p > 0.05$) or each other ($p > 0.05$). These results suggest that reaction times below 100ms (because of slow random, repetitive or anticipatory responses) were different after running. Specifically, the results suggest that perseveration errors increased in a linear fashion with

exercise intensity. However, the errors made after low, moderate and high intensity running were not specifically different from each other.

Figure 29: Perseveration post running
Note. The x-axis represents the 4 conditions, baseline, low intensity, moderate intensity and high intensity post running. On the y-axis the amount of perseveration errors is shown. The overall repeated-measures ANOVA was significant and Bonferroni adjusted post-hoc measures indicated no particular differences.

Reaction Time Block Change

A one-way within subjects (or repeated measures) ANOVA was conducted to compare the effect of exercise intensity on reaction time block change. Reaction time block change values were -0.0044 ± 0.017, 0.0074 ± 0.014, 0.0056 ± 0.016 and 0.011 ± 0.012 for resting, low, moderate and high intensity, respectively. Mauchly´s test indicated that the assumption of sphericity had not been violated ($\chi^2(5) = 1.21$, $p > 0.05$); therefore degrees of freedom were not corrected. The overall result from the one-way repeated measures (within subjects) ANOVA showed that reaction time block change was significantly affected by Exercise Intensity $F(3, 78) = 5.57$, $p < 0.005$, $\eta p2 = 0.18$. Observed power was .93. Polynomial trend analyses showed a significant linear increase in reaction time block change with increasing exercise intensity $F(1,26) = 13.82$, $p < 0.005$, $\eta p2 = 0.35$ with a power of .95. Bonferroni corrected, pairwise comparisons indicated that reaction time block change at baseline was only significantly different from the values after high intensity exercising ($p < 0.005$). All other comparisons were not significantly different from one another ($p > 0.05$). These results suggest that the change in reaction time throughout the duration of the CCPT test was different after running.

Specifically, the results suggest that reaction time during the test slowed more after higher intensity running. Especially after high intensity the reaction time increased throughout the test more than in the other intensity conditions.
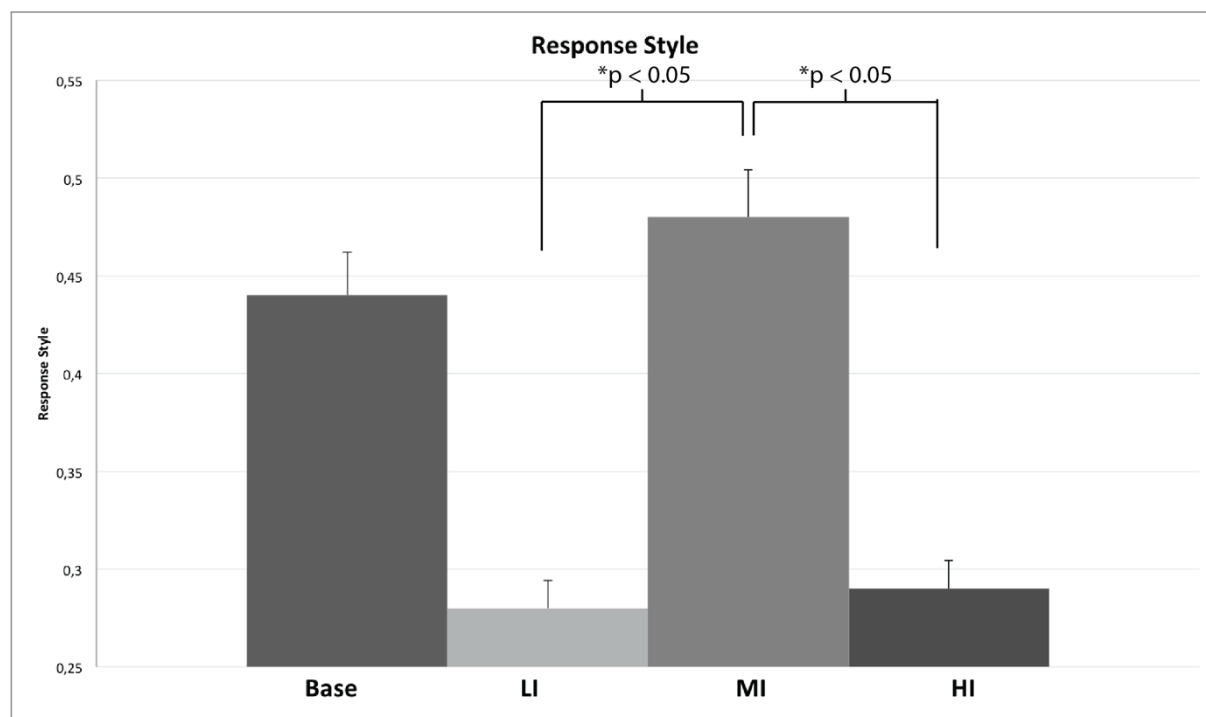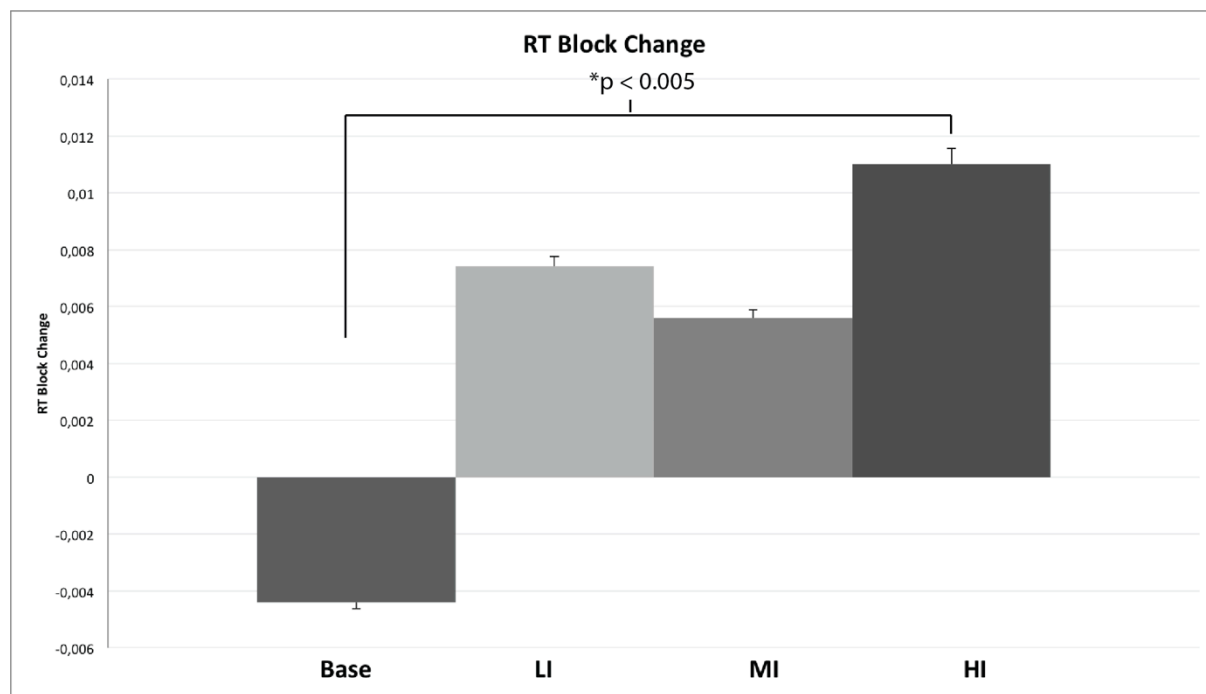

Figure 30: Reaction Time Block Change post running
Note. The x-axis represents the 4 conditions, baseline, low intensity, moderate intensity and high intensity post running. On the y-axis a measure of reaction time block change is shown. The overall repeated-measures ANOVA was significant and Bonferroni adjusted post-hoc measures indicated that reaction time block change at baseline was different from reaction time block change after high intensity running.

Reaction Time Standard Error Block Change

A one-way within subjects (or repeated measures) ANOVA was conducted to compare the effect of exercise intensity on reaction time standard error block change. Reaction time standard error block change values were 0.011 ± 0.084, 0.046 ± 0.055, 0.033 ± 0.063 and 0.057 ± 0.073 for resting, low, moderate and high intensity, respectively. Mauchly´s test indicated that the assumption of sphericity had not been violated ($\chi^2(5) = 4.69$, $p > 0.05$); therefore degrees of freedom were not corrected. The overall result from the one-way repeated measures (within subjects) ANOVA showed that reaction time standard error block change was significantly affected by Exercise Intensity $F(3, 78) = 3.20$, $p < 0.05$, $\eta p2 = 0.11$. Observed power was .72. Polynomial trend analyses showed a significant linear increase in reaction time standard error block change with increasing exercise intensity $F(1,26) = 5.37$, $p < 0.05$, $\eta p2 = 0.17$ with a power of .61. Bonferroni corrected, pairwise comparison indicated that reaction time standard error block change was not significantly different in any condition ($p > 0.05$). These results suggest that the change in response consistency during the time course of the test was

different after running. Specifically, the results suggest that response consistency got impaired in a linear fashion with intensity after running.
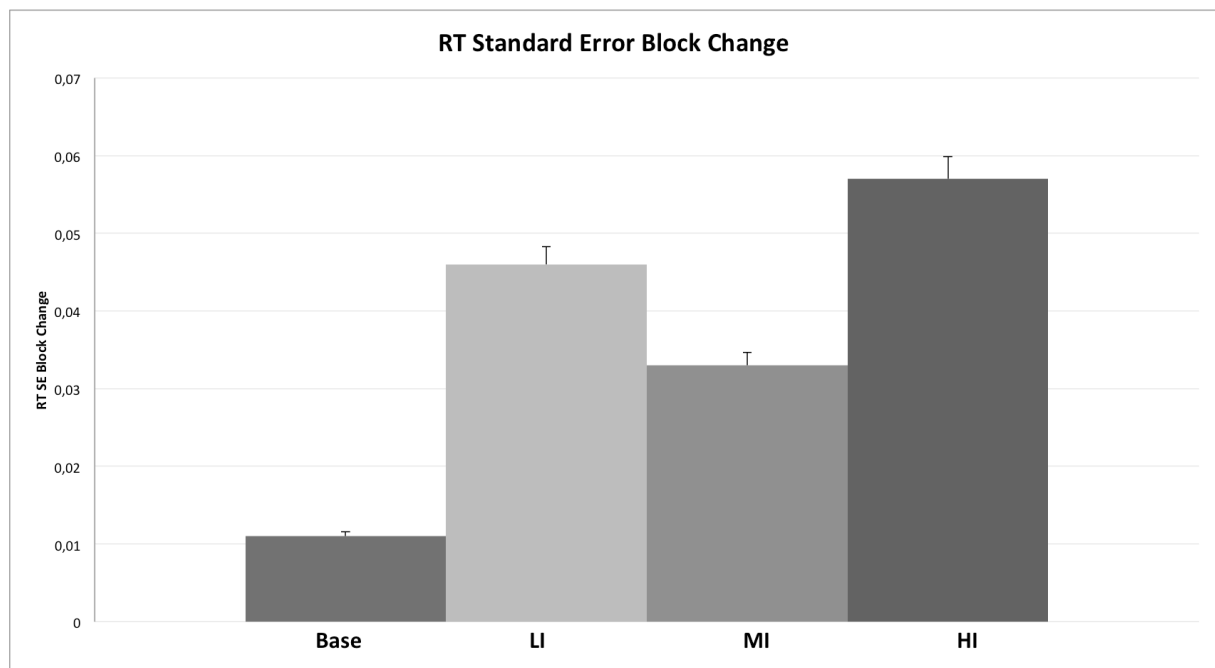
Figure 31: Reaction Time Standard Error Block Change post running
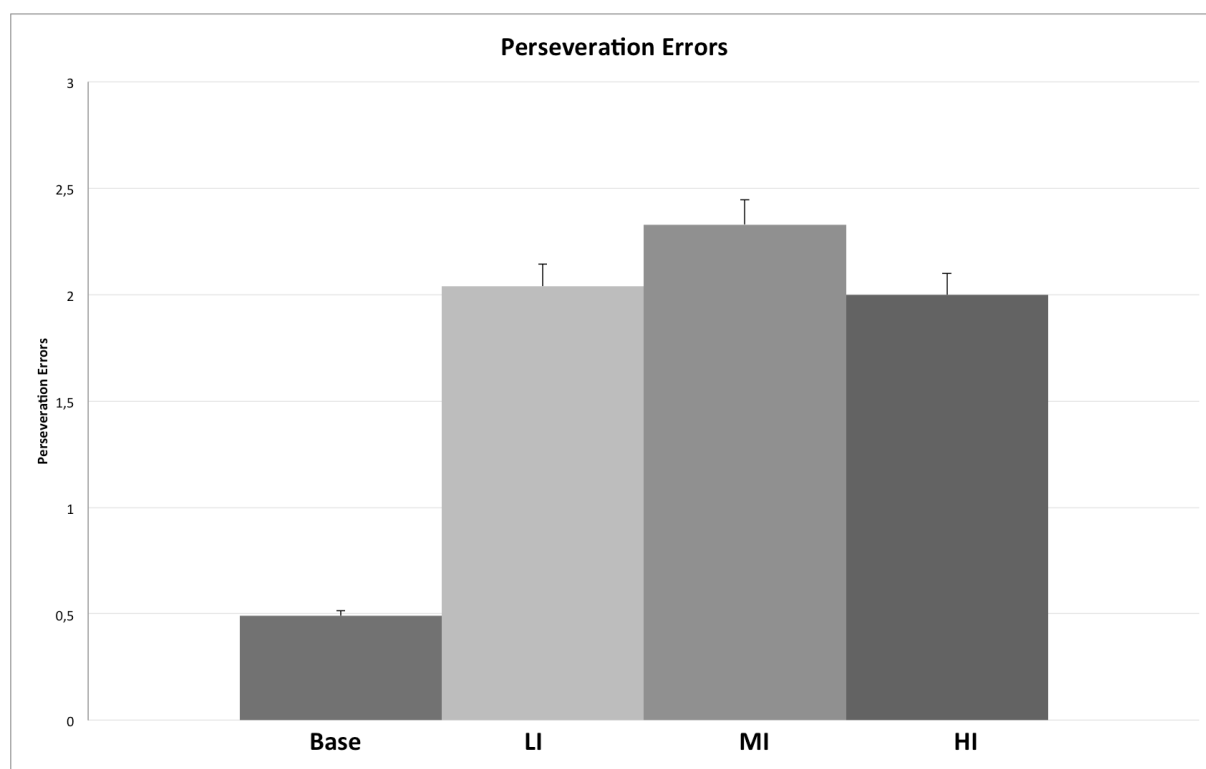Note. The x-axis represents the 4 conditions, baseline, low intensity, moderate intensity and high intensity post running. On the y-axis a measure of reaction time standard error block change is shown. The overall repeated-measures ANOVA was significant and Bonferroni adjusted post-hoc measures indicated no particular differences.

3.2.2   PANAS

Positive Affection after High Intensity Interval Training

Paired-sample t-tests were conducted to see differences in PA or NA before and after LI, MI or HI bouts of exercise that were isocalorifically matched. The statistics revealed a significant difference only in PA before (13.52 ± 4.14) and after (15.22 ± 4.24) the HI Interval Training session in the post phase of the study; $t(26) = -2.13$, $p < 0.05$.
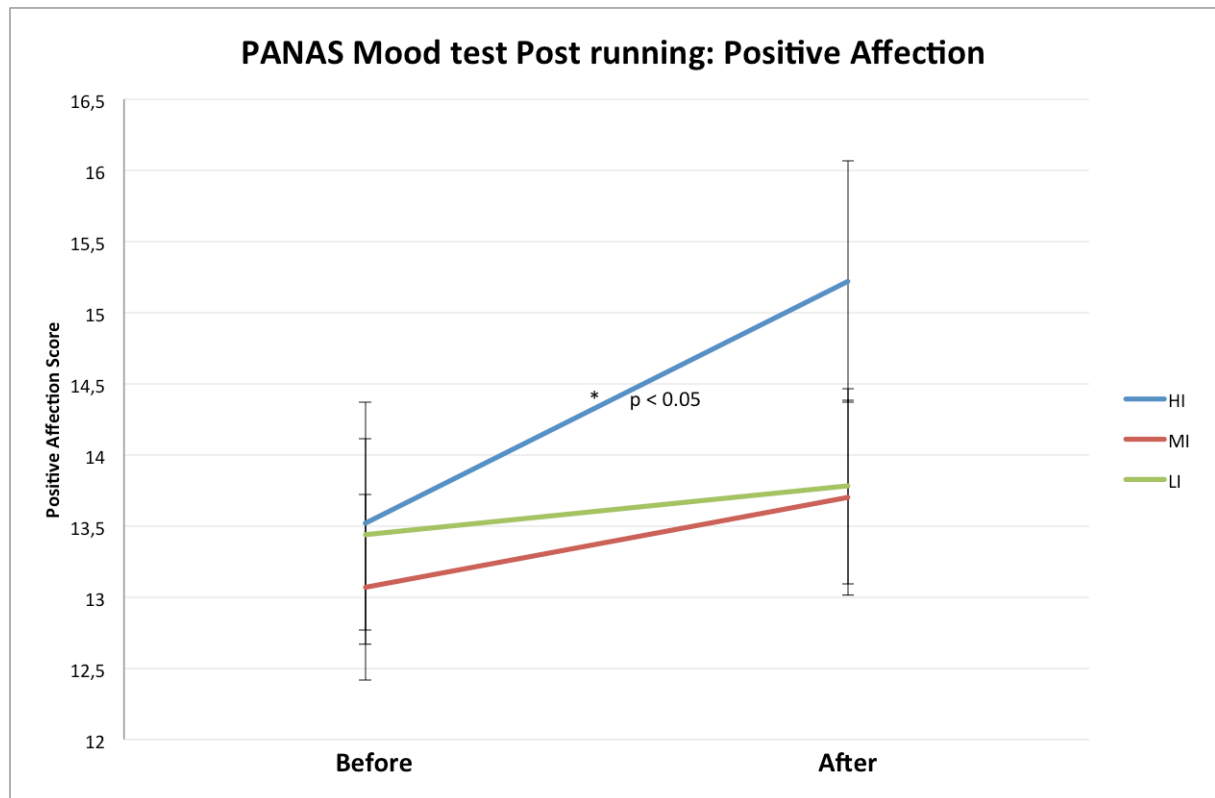
Figure 32: Positive Affection Before and After running at low, moderate and high intensity
Note. The x-axis shows the condition before and after running. The y-axis indicates the score of the positive affection assessed by the Positive Affection Negative Affection mood score. The green line represents the change in the score before and after low intensity treadmill running, the red line represents the change in the score before and after moderate intensity treadmill running and the blue line shows the difference in the score before and after high intensity treadmill running. Only the high intensity changed the positive affection score. The significance level was determined as $p < 0.05$.
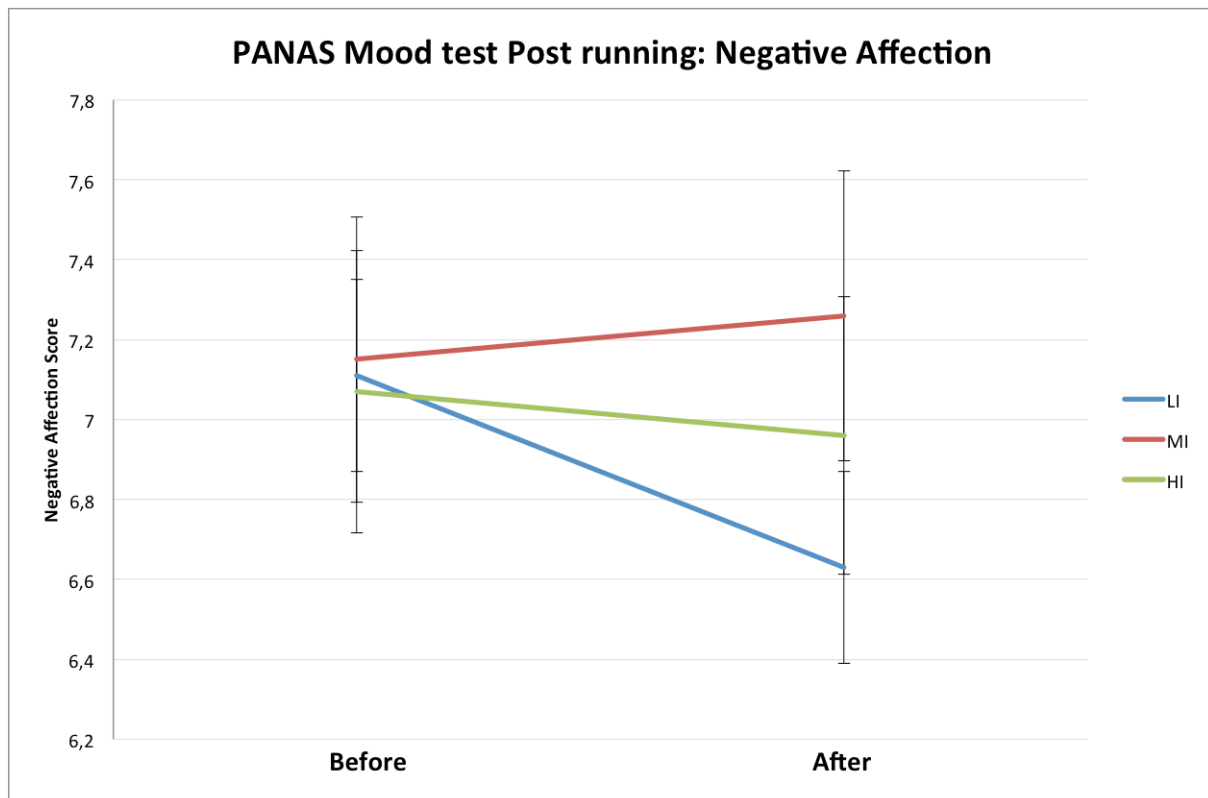
Figure 33: Negative Affection Before and After running at low, moderate and high intensity
Note. The x-axis shows the condition before and after running. The y-axis indicates the score of the negative affection assessed by the Positive Affection Negative Affection mood score. The green line represents the change in the score before and after low intensity treadmill running, the red line represents the change in the score before and after moderate intensity treadmill running and the blue line shows the difference in the score before and after high intensity treadmill running. None of the conditions were significant. The significance level was determined as $p < 0.05$.

It was further investigated whether the observed change in PA affection (mood) after HI exercise was associated with the differential change in CPT performance from baseline to after HI exercise. For this assessment, Pearson´s correlation coefficient analyses were conducted between individuals´ differential positive affect score and corresponding differential scores in the CCPT performance parameters. This analysis was limited to PA in the HI session because that was the only score shown to have significant differences and to the CCPT variables RT, Commission Errors, Reaction Time Block Change, Response Style and because those variables were shown by Bonferroni adjusted post-hoc analyses to have particular changes after the HI exercise session. In addition to those CCPT performance parameters, the ratio between reaction time and commission errors to normalize reaction time to the commission errors made in that condition was calculated and tested for correlation with PA. Also commission errors alone were analysed for correlation with PA. The positive affect change score was correlated with the change scores in CCPT performance which was extracted numerically by subtracting performance after HI exercise from performance at baseline: $(PA_{post} - PA_{pre})$ with $(CCPTscore_{post} - CCPTscore_{pre})$. A Pearson correlation coefficient between affect and any of the

CCPT performance measures (including the calculated ratio) was computed to assess the relationship between CCPT performance and mood. There was a no significant correlation between PA and any of the CCPT performance variables, $-.12 < r > .136$, $n = 27$, $p > 0.05$. Table 6 summarizes the results Overall, there was no positive or negative correlation between PA and CCPT performance after high intensity running.

Correlations

		RTHI	COHI	RatioHI	RTBlockChangeHI	PeseverationErrHI	PAHI
RTHI	Pearson Corr.	1	-.585**	.986**	-.122	-.337	.072
	Sig. (2-tailed)		.001	.000	.543	.086	.720
	N	27	27	27	27	27	27
COHI	Pearson Corr.	-.585**	1	-.712**	-.017	.560**	-.124
	Sig. (2-tailed)	.001		.000	.931	.002	.536
	N	27	27	27	27	27	27
RatioHI	Pearson Corr.	.986**	-.712**	1	-.102	-.407*	.088
	Sig. (2-tailed)	.000	.000		.611	.035	.662
	N	27	27	27	27	27	27
RTBlockChangeHI	Pearson Corr.	-.122	-.017	-.102	1	.261	.136
	Sig. (2-tailed)	.543	.931	.611		.189	.498
	N	27	27	27	27	27	27
PeseverationErrHI	Pearson Corr.	-.337	.560**	-.407*	.261	1	-.012
	Sig. (2-tailed)	.086	.002	.035	.189		.953
	N	27	27	27	27	27	27
PAHI	Pearson Corr.	.072	-.124	.088	.136	-.012	1
	Sig. (2-tailed)	.720	.536	.662	.498	.953	
	N	27	27	27	27	27	27

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Table 6: Correlations of positive affection and CCPT performance variables
Note. The table shows correlations between the change in reaction time (RTHI), commission errors (COHI), the ratio between them (RatioHI), reaction time block change (RTBlockChangeHI), perseveration errors (PeseverationErrHI) and the change in positive affection before and after high intensity interval training. None of the comparisons with PAHI were significant. Table is from the SPSS output.

3.3   Gender, Age and VO$_{2max}$

Baseline: Independent-samples t-tests were conducted to compare reaction time, commission error, reaction time standard error, hit reaction time ISI change, response style, perseveration error, reaction time block change or standard error block change in male and female; higher and lower age or higher and lower VO$_{2max}$ **at baseline**. The threshold for grouping of the participants into higher and lower age

or VO_{2max} was achieved by the median of the respective variable. If significant, Levene´s test for equality of variances was used to correct the p-value for unequal variances. There were no significant differences in any of the conditions (all p´s > 0.05). However, grouping participants in lower (295.48 ± 29.58ms) and higher age (322.81 ± 44.09ms) for reaction time at baseline showed a almost significant age effect on reaction time which, more specifically, seemed to increase with age; t(28)=1.993, p = 0.056. These results suggest that at baseline, Gender, Age and VO_{2max} did not have an effect on the CCPT performance variables that were shown to be affected by exercise intensity.

Gender

Within-subject repeated measure ANOVA with gender as a between-subject factor was conducted to see if gender had an effect on those performance variables that were shown (see above) to be affected by exercise intensity in either the during running or in the post running condition.

During: Mauchly´s test indicated that the assumption of sphericity had not been violated ($\chi^2(2) = 1.716$, p > 0.05); therefore degrees of freedom were not corrected. The overall result from the interaction of *gender* and **commission error** in the one-way repeated measures (within subjects) ANOVA with gender as a between-subject factor showed that commission error made in during running differed significantly between male and female participants F(2, 56) = 6.920, p < 0.005, ηp2 = 0.20. Observed power was .91. Due to low power post-hoc tests with adjusted p-values (p / conditions) were not calculated.

Figure 34: Effect of Gender on commission error at rest and during running on low or moderate intensity
Note. The x-axis represents males and females during three different intensity conditions. In the y-axis the amount of commission errors is shown. Dark and light blue bars represent commission errors of males and females, respectively made at baseline. Red and orange shows the commission errors of males and females, respectively during low intensity running. Dark green and light green indicates commission errors of males and females, respectively during moderate intensity running. The overall repeated-measures ANOVA model was significant for commission errors with gender as an in-between subjects factor.

Post: Mauchly´s test indicated that the assumption of sphericity had not been violated ($\chi^2(5) = 5.609$, $p > 0.05$); therefore degrees of freedom were not corrected. The overall result from the interaction of *gender* and **standard error block change** in the one-way repeated measures (within subjects) ANOVA with gender as a between-subject factor showed that standard error block change post running differed significantly between male and female participants $F(3, 75) = 2.851$, $p < 0.05$, ηp2 = 0.10. Observed power was .66.
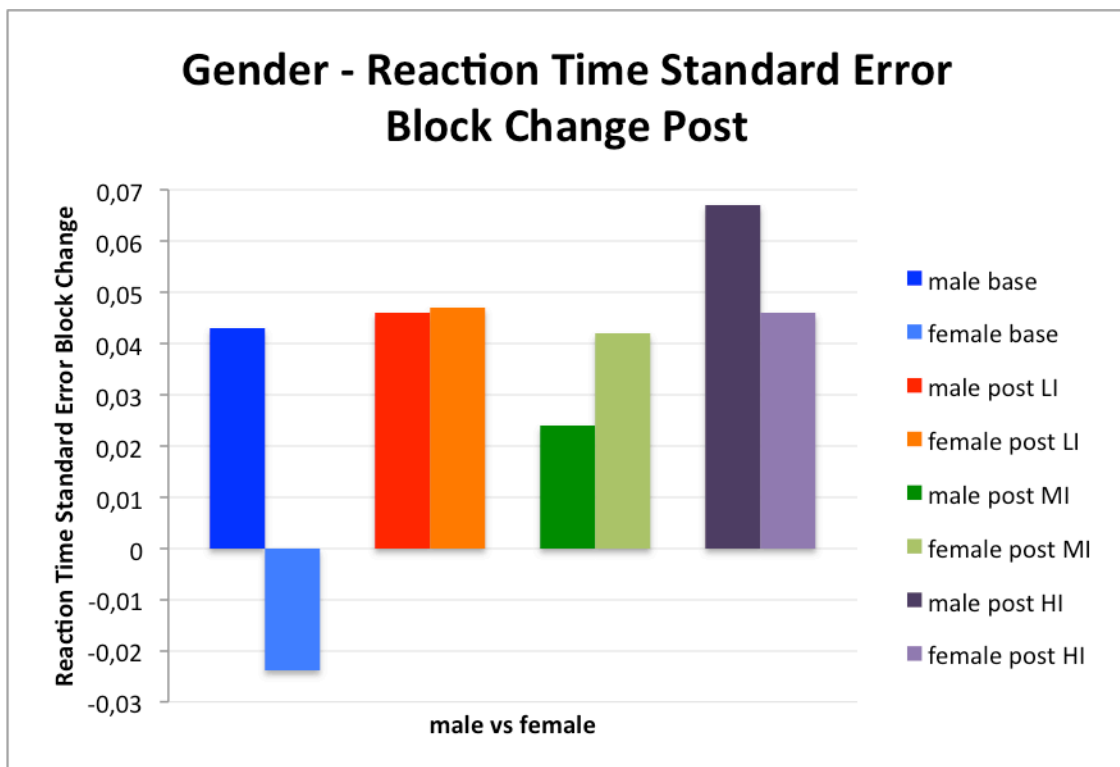
Figure 35: Effect of Gender on reaction time standard error block change at rest and post running on low, moderate or high intensity
Note. The x-axis represents males and females during four different intensity conditions post running. In the y-axis a measure of reaction time standard error block change is shown. Dark and light blue bars represent reaction time standard error block change of males and females, respectively made at baseline. Red and orange show the reaction time standard error block change of males and females, respectively after low intensity running. Dark green and light green indicate reaction time standard error block change of males and females, respectively after moderate intensity running. Dark and light purple represent reaction time standard error block change of males and females, respectively after high intensity training. The overall repeated-measures ANOVA model was significant for reaction time standard error block change with gender as an in-between subjects factor.

Age

Within-subject repeated measure ANOVA with age as a between-subject factor was conducted to see if age had an effect on those performance variables that were shown to be affected by exercise intensity in either the during running or in the post running condition.

Post: Mauchly´s test indicated that the assumption of sphericity had not been violated ($\chi^2(5) = 2.120$, $p > 0.05$); therefore degrees of freedom were not corrected. The overall result from the interaction of

age and **reaction time block change** in the one-way repeated measures (within subjects) ANOVA with age as a between-subject factor showed that reaction time block change post running differed significantly between young and old participants $F_{(3, 75)} = 5.381$, $p < 0.05$, ηp2 = 0.10. Observed power was .66.
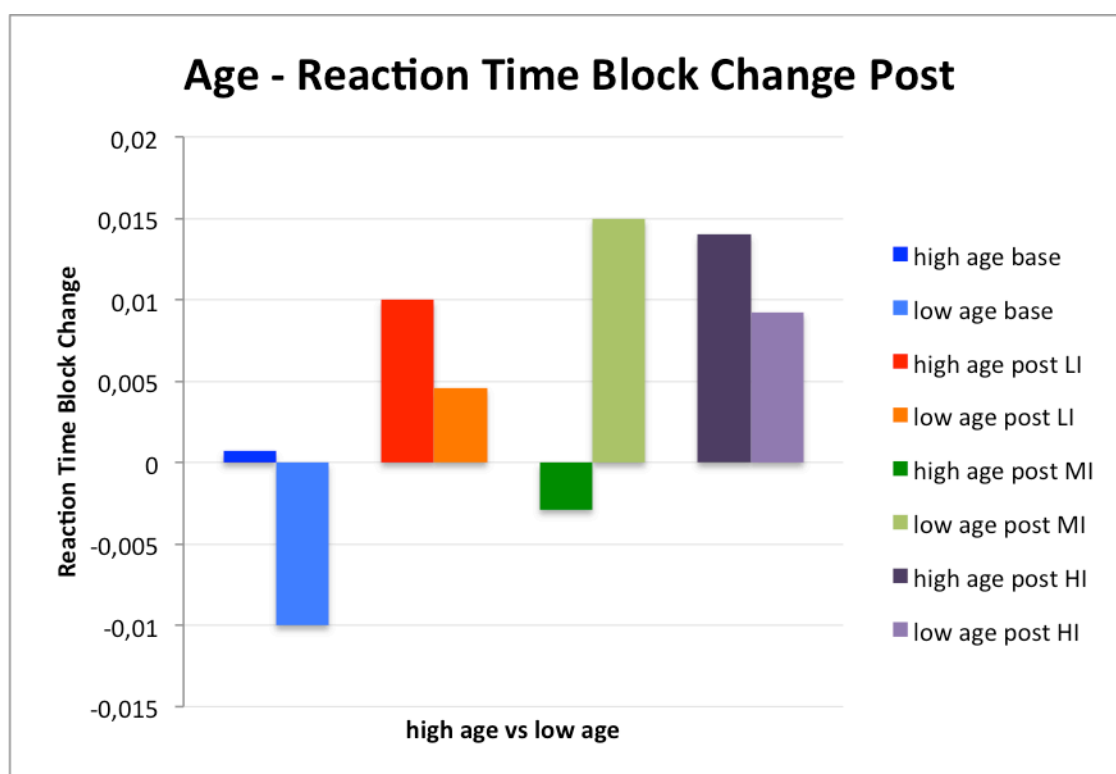
Figure 36: Effect of Age on reaction time standard error block change at rest and post running on low, moderate or high intensity
Note. The x-axis represents high and low age group during four different intensity conditions post running. Since the study consisted of young, healthy people, the high age group represents subjects in their late twenties whereas the low age group consists of subjects in their early twenties. In the y-axis a measure of reaction time block change is shown. Dark and light blue bars represent reaction time block change of high and low age, respectively made at baseline. Red and orange show the reaction time block change of high and low age, respectively after low intensity running. Dark green and light green indicate reaction time block change of high and low age, respectively after moderate intensity running. Dark and light purple represent reaction time block change of high and low aged subjects, respectively after high intensity training. The overall repeated-measures ANOVA model was significant for reaction time block change with age as an in-between subjects factor.

During: Age had no interaction for the during running results. However, age seemed to have a tendency to interact with reaction time during running. Mauchly´s test indicated that the assumption of sphericity had not been violated ($\chi^2(2) = 1.884$, $p > 0.05$); therefore degrees of freedom were not corrected. The overall result from the interaction of *age* and **reaction time** in the one-way repeated measures (within subjects) ANOVA with age as a between-subject factor showed that reaction time during running differed between younger and older participants $F_{(2, 56)} = 3.062$, $p = 0.055$, ηp2 = 0.10 but did not reach statistical significance. Observed power was .57.
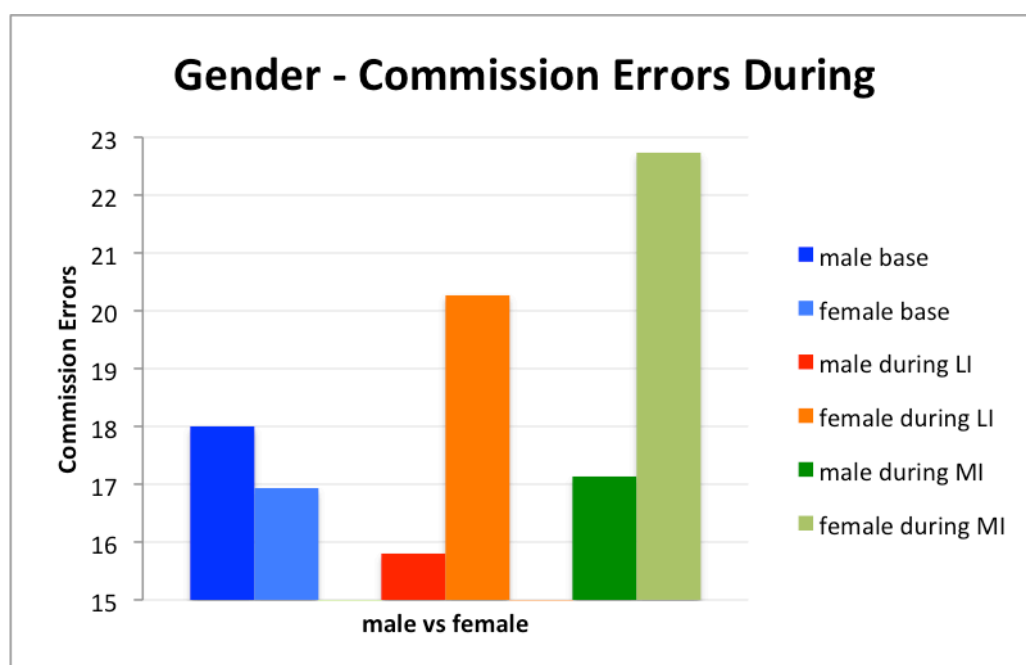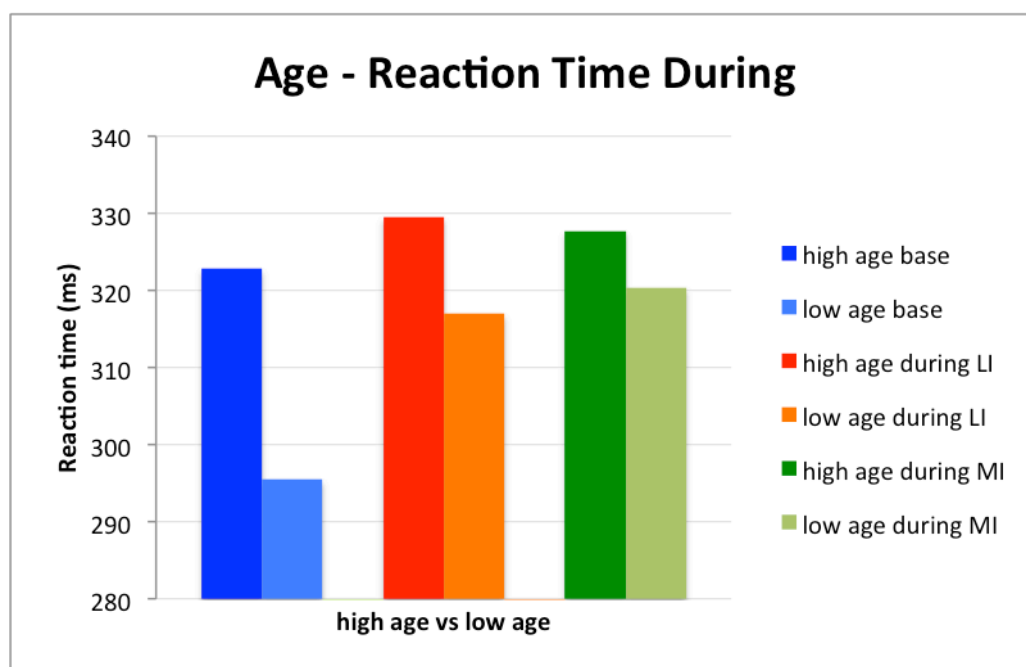
Figure 37: Effect of Age on commission error at rest and during running on low /moderate intensity
Note. The x-axis represents high and low age group during three different intensity conditions. Since the study consisted of young, healthy people, the high age group represents subjects in their late twenties whereas the low age group consists of subjects in their early twenties. In the y-axis reaction time is measured in milliseconds. Dark and light blue bars represent reaction time of high and low age, respectively made at baseline. Red and orange bars show the reaction time of high and low age, respectively during low intensity running. Dark and light green indicate reaction time of high and low age, respectively during moderate intensity running. The overall repeated-measures ANOVA model was significant for reaction time with age as an in-between subjects factor.

VO$_{2max}$

Differences in VO$_{2max}$ did not have a different effect on CCPT performance during or post running on different intensities (all p´s > 0.05). However, there was a trend for an influence of *VO$_{2max}$* values on **commission error** F(2, 56) = 2.936, p = 0.061, ηp2 = 0.06 **during** running (Sphericity assumed, X^2(2) = 1.622, p > 0.05). Observed power was .55.
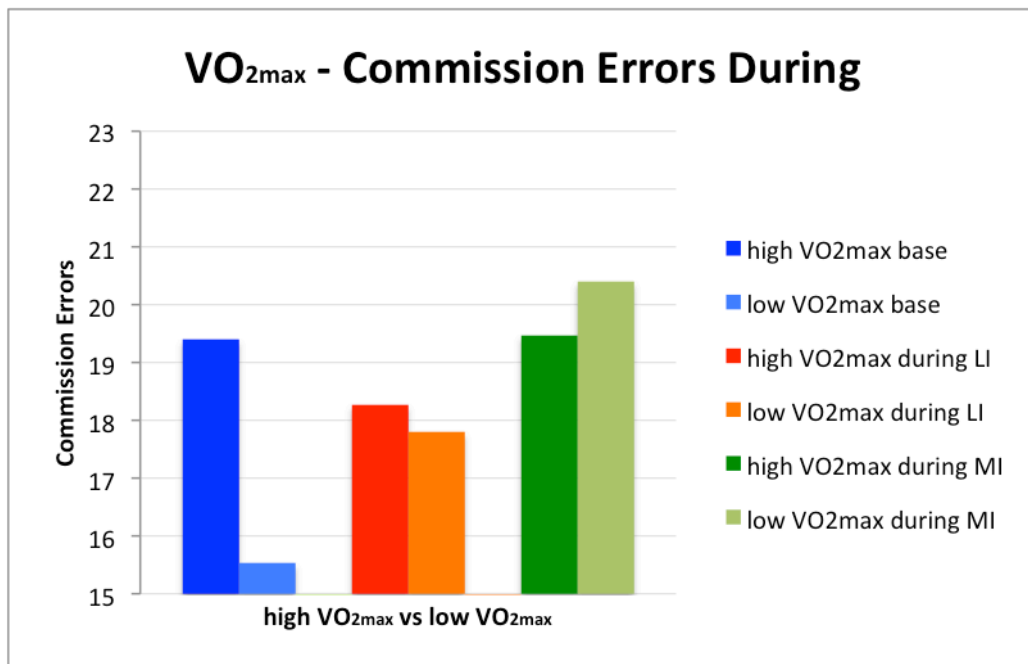
Figure 38: Effect of VO$_{2max}$ on commission error at rest and during running on low or moderate intensity
Note. The x-axis represents a high and low VO$_{2max}$ group during three different intensity conditions. In the y-axis the amount of commission errors are shown. Dark and light blue bars represent commission errors of the high and low VO$_{2max}$ group, respectively made at baseline. Red and orange bars show commission errors of the high and low VO$_{2max}$ group, respectively during low intensity running. Dark and light green indicate commission errors of the high and low VO$_{2max}$ group, respectively during moderate intensity running. The overall repeated-measures ANOVA model reached a value close to significance for commission errors with VO$_{2max}$ as an in-between subjects factor.

3.4   Results TMS & tDCS

Preliminary results (n=4) from a paired, two-tailed t-test show that cathodal tDCS at rest led to a decrease in reaction time (from 313.22 ± 21.98ms to 296.36 ± 35.46ms; $p=0.09$) and to a significant increase in commission errors (from 15.75 ± 8.38 to 21.25 ± 10.31; $p<0.05$) compared to at baseline.
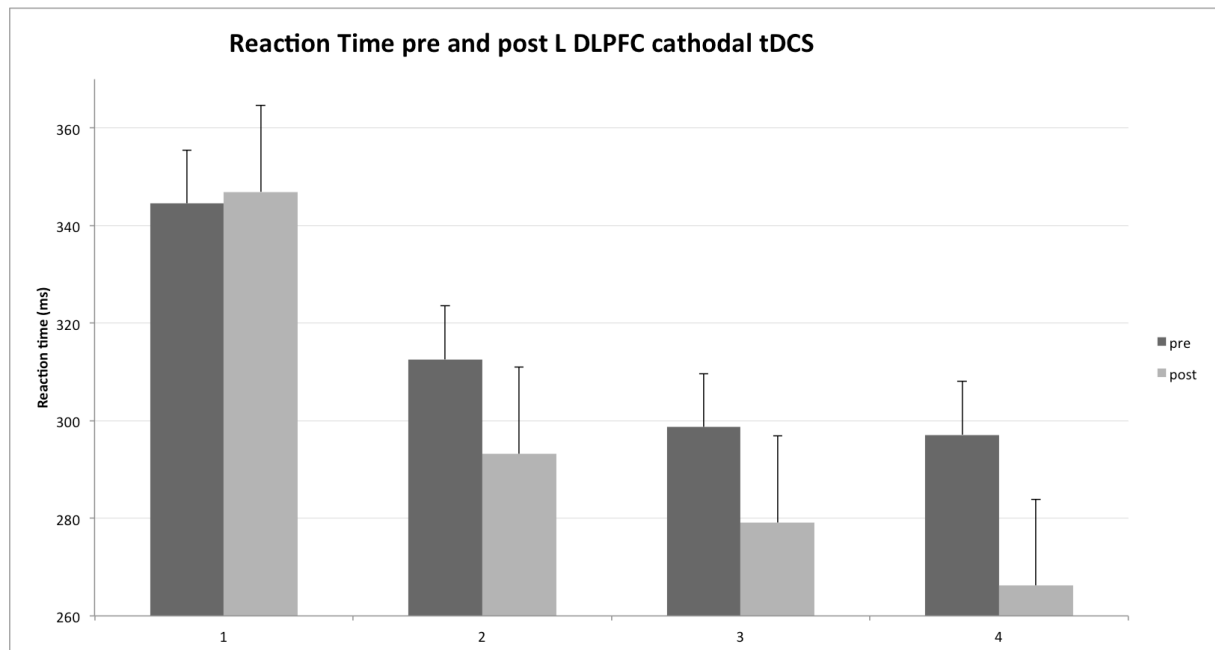
Figure 39: Reaction Time before and after cathodal tDCS over the left DLPFC
Note. The x-axis shows single subjects. The y-axis shows reaction time in milliseconds. The dark bars represent the values before and the grey bars the values after transcranial direct current stimulation with the cathode over the left dorsolateral prefrontal cortex and a right supraorbital anode. The paired t-test showed that this results is close to significance ($p = 0.09$).
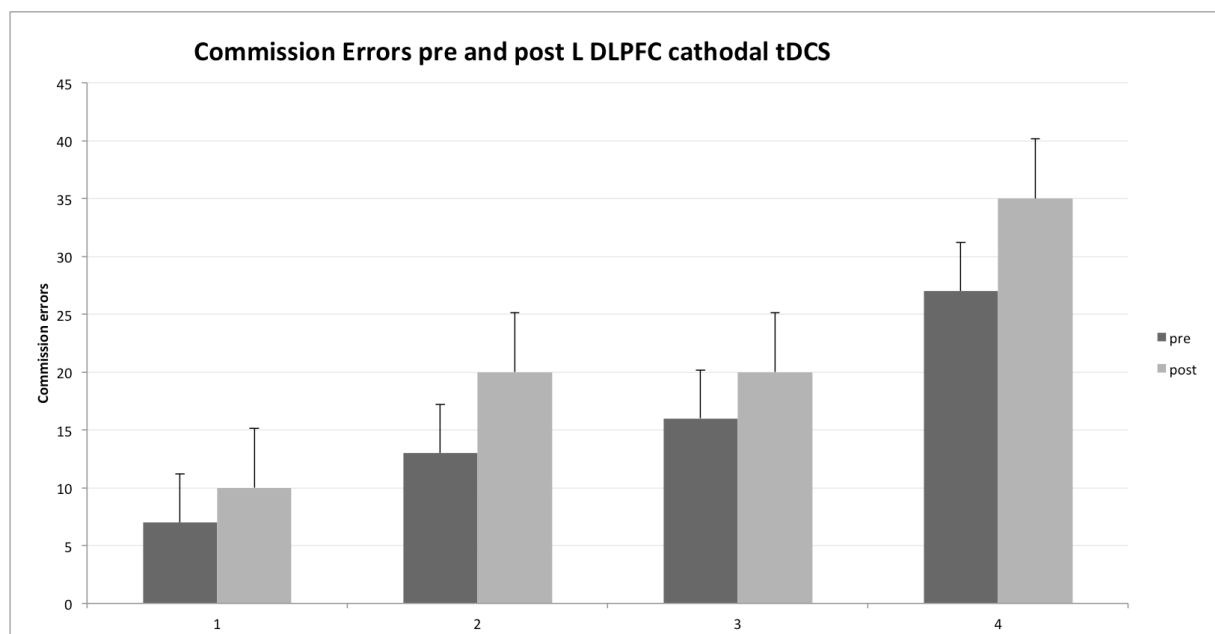
Figure 40: Commission Error before and after cathodal tDCS over the left DLPFC
Note. The x-axis shows single subjects. The y-axis shows the amount of commission errors. The dark bars represent the values before and the grey bars the values after transcranial direct current stimulation with the cathode over the left dorsolateral prefrontal cortex and a right supraorbital anode. The paired t-test showed that this results is significance ($p < 0.05$).

Other data shows that post running alone decreased reaction time (254.48ms) and increased commission errors (24 commission errors) more than cathodal tDCS at rest (260ms and 19 commission errors, respectively) and cTBS post running decreased reaction time (250.13ms) and increased the amount of commission errors (27 commission errors) in one subject even more than post running alone. Anodal tDCS post running (301.21ms; 16 commission errors) did not replicate resting values (344.51ms 7 commission errors).

Moreover, the amplitude of motor evoked potentials in two subjects was 3.97 and 1.35 times higher immediately after running exercise compared to before running (from 1.30 to 5.17 and 1.02 to 1.37, respectively).

4   Discussion

The goal of the present study was to investigate the effect of exercise intensity on executive and attentional control using the Conners Continuous Performance Test (CCPT). The main overall result is a non-intensity dependent increase in processing time and a non-significant trend for an intensity-dependent increase in impulsivity errors during running whereas post running, a decrease in processing time is paired with an increase in impulsivity errors measured by commission errors. These findings suggest that the computational demand of running impairs executive function. In particular, response inhibition, whose brain circuits are embedded in the executive network of the explicit information processing system of highest computation order in the prefrontal cortex, appears to be affected by running, in an intensity dependent fashion, immediately at the onset of exercise, which may be imposed by a state of hypofrontality. A state of hypofrontality is also observable in the executive, inhibition network post running exercise whereas processing time was facilitated in a intensity dependent fashion pointing towards an instinct-based response style post exercise. A summary of all the CCPT performance variables is presented in table 7. Preliminary TMS & tDCS results show that the state of post exercise could be both, reproduced by cathodal tDCS over the left DLPFC, and pronounced by continuous theta burst stimulation (cTBS). However, anodal tDCS after running was not able to reverse running effects, pointing towards different mechanisms active during running and recovery and underlining the strong effects of running exercise, which also increased primary motor cortex (M1) excitability, possibly implying an association between a state of hypofrontality and central fatigue.

CCPT Variables	Rest	During		Post		
		Low	*Moderate*	*Low*	*Moderate*	*High*
RT *#	309,15 ± 39,42	323,24 ± 34,11	324,07 ± 34,44	284,31 ± 34,54	279,66 ± 31,92	275,23 ± 29,36
COM	17,47 ± 7,38	18,03 ± 8,89	19,93 ± 8,82	19,07 ± 7,9	20,37 ± 7,99	19 ± 8,33
Omission	3,77 ± 4,46	3,57 ± 4,15	4,5 ± 6,67	2,11 ± 2,01	3,19 ± 2,73	2,19 ± 1,84
RTStdErr *	4,19 ± 1,21	3,64 ± 0,97	3,74 ± 1,05	3,54 ± 0,92	3,71 ± 1,02	3,97 ± 1,92
Detectability	0.53 ± 0.32	0,55 ± 0,38	0,49 ± 0,45	0,47 ± 0,31	0,45 ± 0,31	0,53 ± 0,41
Variability	6,23 ± 4,34	4,87 ± 2,08	5,48 ± 3,39	4,86 ± 1,73	5,97 ± 2,91	6,93 ± 8,13
Response Style #	0,43 ± 0,40	0,50 ± 0,45	0,51 ± 0,75	0,28 ± 0,22	0,48 ± 0,38	0,29 ± 0,30
Perseveration #	0,67 ± 1,35	2,73 ± 6,03	1,93 ± 4,48	2,04 ± 2,9	2,33 ± 4,16	2 ± 2,75
RT Block Change #	-0,0033 ± 0,017	-0,001 ± 0,015	-0,0023 ± 0,017	0,0074 ± 0,014	0,0056 ± 0,016	0,012 ± 0,013
RT ISI change *	0,035 ± 0,023	0,043 ± 0,023	0,044 ± 0,02	0,042 ± 0,02	0,045 ± 0,028	0,045 ± 0,023
RT SE Block Change #	0,016 ± 0,083	0,023 ± 0,066	0,014 ± 0,07	0,046 ± 0,055	0,033 ± 0,063	0,057 ± 0,073
RT SE ISI change	-0,023 ± 0,12	-0,056 ± 0,1	-0,052 ± 0,14	-0,028 ± 0,089	-0,0093 ± 0,15	0,0037 ± 0,12

Table 7: Overview over all CCPT performance variables at rest, during and post running
Note. The description of the variables of the Conners Continuous Performance test is given in table 2. RT stands for reaction time, COM for commission error, RTStdErr for reaction time standard error, ISI for interstimuli interval, SE for standard error. The performance variables that were significant different from baseline during running are marked with *. Performance variables that were significant post running are marked with #.

4.1   Discussion During

4.1.1   CCPT Performance Variables

During low intensity exercise it was found that exercise had an impairing effect on reaction time and reaction time ISI change (increase) in a linear increasing fashion with intensity but no significant differences between low and moderate exercise intensity were found in post-hoc analyses. Reaction time standard error was also affected by exercise intensity in a quadratic fashion with low intensity being different from baseline, showing lowest values. Commission errors, indicating response inhibition, did not change significantly but showed a strong trend (p=0.57) to increase with exercise in an intensity dependent fashion. The non-significant result is very likely due to low statistical power.

Increased reaction time ISI change indicates that reaction time got slower with increases in ISI, thus adjustments to different ISI was impaired, in a linear fashion with intensity. In practical terms this might indicate an analogue to adjusting to new game situations in a variety of sports. Reaction time standard error depicts consistency of response speed and erractiness, thus perceptual and discrimination power between targets and non-targets and was shown to be improved in the low intensity condition compared to baseline. The fact that all stated performance variables worsened during exercise with the exception of reaction time standard error might be due to the so-called floor effect. It describes the facilitation effect of physical exercise on reaction speed, which primarily influences slower reaction times, thus reducing differences between faster and slower reaction times and increasing consistency (Pesce et al. 2003). Increased reaction time and therefore processing time paired with a strong trend for an increase in commission errors during running implies a state of hypofrontality (Dietrich 2003) that was evident already during 14min of treadmill running. This points towards an immediate computational challenge of running at the onset of exercise that does not need hours to become evident and the fact that reaction time (intrinsic) was not different between low and moderate intensity running might imply no computational difference between intensities. Since commission errors seemed to be rather intensity-dependent impaired exercise intensity must have still affected response inhibition, most likely in a metabolic-driven pathway.

Previous research showed decrements in cognitive function during exercise (Davranche & McMorric 2009; Mahoney et al. 2007; Paas & Adam 1991; Pontifex & Hillman 2007). Nevertheless, a recent meta-analysis (Chang et al. 2012) concludes a small positive overall effect of exercise on cognitive function during exercise. More particularly, studies varying intensity and length of exercising show facilitation effects on reaction time during cycling (Adam et al. 1997; Arcelin et al. 1998; Davranche & Audiffren 2004; Davranche et al. 2005; Davranche et al. 2006; Audiffren et al. 2008). However, Reaction time during running in this study was not decreased but instead increased. This is very likely due to a higher demand of computational resources during running compared to cycling, the type of

exercise used in the other studies. The literature of studies using running as the chosen exercise mode is rare.

Even though in their study Collardeau et al. (2001) conclude a cognitive improvement effect of running exercise, the mean simple reaction time of 8 well-trained triathletes increases during running and even reaches significance during the first of two tests during running, similarly to the finding of the present study. The stated positive effect of running on reaction time (Collardeau et al. 2001) is likely due to their findings of decreased simple (only significant in the CHO hydrated group) and choice (not significant) reaction times post running, which resemble our findings well, even if one disregards their additional hydration effect. Unfortunately in their study choice reaction time, which was also increased in our study, was not recorded during the 100min of running at ventilator threshold. Such an investigation could proof the functional hierarchy of cognition (Dietrich 2003), which would predict decrements even in the lower centres during a prolonged exercise bout (Cian et al. 2000). Hence, the higher computational of running in the present study not only impairs the highest order executive control but also to lower levels of implicit information processing (see figure 7). Consequently, the computational demand of running (consider the computation complexity of the tibia muscle) might overshadow the effects the reticular activating systems that are hypothesized (Dietrich & Audiffren 2011) to account for the decrease in reaction time in the studies showing a decrease in reaction time during cycling. Another explanation for an increase in reaction time might be reduced cerebral blood flow (Ando et al. 2005). An increase in simple RT task was shown during an incremental cycling protocol but only when participants were above VT with no effect post exercise (Ando et al. 2005). Still, a general weakness with incremental protocols is that intensity effects are difficult to extract due to exercise time and/or intensity effects of the immediate prior intensities. Therefore, the cognitive state constantly changes (Dietrich 2009). Even in the present study with fixed intensities, a dynamic of information processing could be observed within the test duration. In a later study with more distinct exercise intensities, Ando et al. (2011) associated a decrease in choice reaction time (more particularly, pre-motor time) during a modified version of the Eriksen flanker task whilst cycling at 60% VO_{2peak} with no change in cerebral oxygenation measured in the right frontal cortex using near-infrared-spectroscopy whereas cycling at 80% VO_{2peak} led to a decrease in cerebral oxygenation, which was related to no change in choice reaction time. The result of the first study (Ando et al. 2005) is in line with our findings of increased reaction time and the second study (Ando et al. 2011) points towards reduced cerebral blood flow in the right PFC during strenuous exercise as a possible mechanism interfering with other factors that together negatively influence processing speed. Strenuous exercise that is related to hyperventilation lowers $PaCO_2$ (partial pressure of CO_2), therefore leading to constriction of arterioles in the brain (Nybo & Rasmussen 2007), which together with arterial de-saturation during strenuous exercise (Nielsen et al. 1999) might be the cause for a decrease in cerebral oxygenation suggesting that oxygen availability is insufficient to meet the metabolic

demand (Ando et al. 2011). In contrast, improvements in premotor time, measured from onset of visual stimulus to muscle activation, during lower intensity might imply other (also other than RAS), cognitive-facilitating factors during low intensity exercise that are also independent of cerebral oxygenation and might get covered up during higher intensities by first mentioned mechanisms. Even though the lack of impairment in RT (Ando et al. 2011) compared to the present study and a similar study (Davranche & McMorris et al. 2009) during high intensity was attributed to the greater simplicity of the task, a higher error rate of accuracy was detected at 80% compared to 60%. Moreover, a tendency for a decrease in motor time during 80% might point towards an involvement of the RAS, which is triggered by afferent feedback (Knaepen et al. 2010) in an intensity-dependent manner and therefore only observable in the 80% condition. However, pedalling at a rate of perceived exertion (RPE) of 12-13 for 15min was shown by 24-channel near-infrared spectroscopy to increase oxyHb levels in the ventral PFC but not in the dorsal PFC and was associated with mood enhancement (Fumoto et al. 2010) pointing towards different oxygenation dynamics in ventral and dorsal PFC regions in response to acute exercise and opposing the result of decreased right PFC cerebral oxygenation (Ando et al. 2011). Interestingly, during and after this exercise period not only powers of alpha bands increased as measured by EEG but also whole blood serotonin. Thus, these two observations might be causally linked (Fumoto et al. 2010) and therefore serve as an explanatory link between RAS and hypofrontality.

Noteworthy, another meta-regression analysis in the field (Lambourne & Toporowski 2010) summarizes an overall impairing effect of exercise on cognition. The difference to the result of the meta-analysis of Chang et al. 2012 are the inclusion criteria, which consisted of young, healthy subjects and only within-subjects, repeated measure designs, therefore better fitting for applications to the present study. Importantly, a lot of studies investigating the effect of exercise on cognition (Brisswalter et al. 1995; McMorris & Keen 1994; Hogervorst et al. 1996; Ando et al. 2005) consisted of a simple reaction time task only. The combination of both, the explicit and implicit system in this study might trigger the involvement of other brain circuits or require additional resources leading to an immediate shift of resources away from the PFC. Tana et al (2010) support this notion by showing that sustained attention in the CCPT might particularly involve the ACC. Moreover, compared to the executive network mainly controlled by the DLPFC the attentional network might additionally involve the parietal cortex. As will be shown further down in the discussion of the analyses of the single blocks this conclusion does not exclude a possible involvement of the reticular activating system.

It is also noteworthy that the implicit and the explicit information processing systems seemed to get differently affected by exercise intensity. While the more basic implicit system, mirrored by reaction time got somewhat protected from further impairments through higher metabolic demand during moderate intensity compared to low intensity, the explicit system seemed to have a more consistent

linear decrease in activity. This "rescue" effect of the evolutionary pivotal function of reaction time from higher intensity impairments is likely due to bottom-up projections from the reticular activating system to structures involved in implicit processing including basal ganglia, cerebellum, supplementary motor area) (Dietrich & Audiffren 2011). In contrast, the higher order processing network of the explicit system seemed to have a transient decrease in activity with intensity in a intensity dependent fashion pointing towards the assumption that intensity must have impaired response inhibition through metabolic pathways. Earlier it has been suggested (Dietrich 2003) that the RAS has only bottom-up effects on the implicit information processing systems. This is in line with our findings and might explain the "protection" effect of reaction time. However, this effect could not overcome the computational challenge of running, which worsened the average cognitive performance of the 14min.

Worsening of executive function during exercise has been suggested several times before. In 2007 Mahoney et al. found impairment of a vigilance task during 30min of walking with and without obstacles and Pontifex & Hillman documented impairment in the Ericksen flanker task during only 6.5min cycling at 60% HR_{max}. Similarly Davranche & McMorris (2009) demonstrated an impairment in the Ericksen flanker task during 30min of cycling at 50% VO_{2max}. Recently Audiffren et al. (2009) reported a strategy shift in the RNG adjacency score during 35min cycling at 90% ventilator threshold (VT). However, none of these studies looked at intensity effects. All these tests can be regarded to involve explicit processing (Dietrich & Audiffren 2011) and thus likely include executive networks. Only two other study tried to look at the influence of exercise intensity on either EEG measures (Brümmer et al. 2011) or executive function during and immediately after 30min of cycling at VT or 75% VT (Del Giorno et al. 2010). In the latter one, assessment of the Contingent Continuous Performance test (CPT) and the WCST revealed impaired executive control during both intensity conditions and only stayed impaired after exercise in the VT cycling condition. With regards to commission errors in the present study the findings of Del Giorno et al. (2010) during cycling fit well with those during running in this study, except that we recorded a trend for an intensity-dependency. Especially the false alarms in the CPT reflect a lack of inhibition during cycling. Moreover, unique errors in the WCST, the inability to adapt when new information is presented, which is a central part of executive control processing (Royall et al. 2002), were elevated during cycling indicating similarities to the elevated reaction time ISI change during running in the current study, which also pointed towards an impaired ability to adjust to different ISI. However, they did not use cognitive measures that are able to assess time dimensions and they just used two different exercise intensities while the current study is able to add more information to the post exercise findings due to the three different exercise intensities used in this study. Del Giorno et al. (2010) suggest that the decrements in cognitive function during exercise might be due to an impaired cerebral metabolic ratio (Dalsgaard 2006), which describes the relationship of oxygen availability in the brain to the amount of substrate

availability. This points towards an intensity-dependent impairment, which was shown in the current study but not in their study. In light of this theory and our results the intensity dependent change of blood flow to the brain might account for these changes.

Using standardized low-resolution brain electromagnetic tomography Brümmer et al. (2011) found an increase in α activity in somatosensory areas (parietal cortex) after a familiar and in frontal areas after an unfamiliar exercise mode after 50% maximal capacity exercising. Frontal activity in response to an unfamiliar exercise is likely due to learning mechanisms whereas a learned skill is represented by increased activity in parietal and motor areas. However, after subjects performed high intensity exercise in their familiar exercise mode (running and hand cycling) a decrease in frontal ß activity was found, pointing towards a deactivation of frontal regions. Interestingly, there was not such a decrease after high intensity cycling, arm crank exercise or isokinetic exercise even though peak heart rate was not different between cycling and running. This supports our notion that computational challenges are different during different exercise modes. Also the highest lactate measures after intense arm cranking paired with no decrease in frontal ß activity might maybe point towards lactate as an additional metabolic substrate for the brain so that brain areas not important for exercise might sustain activity. However, this might also just be due to a lower computational demand of arm cranking. Still, EEG measures were neither incorporated during exercise nor associated with a cognitive test. Furthermore, brain activity in participating areas got reduced in response to automating these movements (Jansma et al. 2001), which both limit the power of the study.

Another study tried to link neuroelectric changes in response to cycling at 60% HR_{max} to the outcome of a modified flanker test with congruent (<<<< or >>>>) or incongruent (<<>><< or >><<>>) trials and found reduced response accuracy during exercise for incongruent but not for congruent trials, for which reaction time was decreased (Pontifex & Hillman 2007). This behavioural change was linked to decreased N1 and N2 amplitudes at parietal sites and globally, respectively, increased amplitudes for the P2 and P3 at frontal and central, and frontal and lateral sites, respectively and longer N2 and P3 latencies. Increased P3 amplitude points towards an allocation of attentional resources in the frontal lobe, whose amount is proportional to its P3 amplitude and its longer latency points towards a delay in cognitive processing speed related to stimulus discrimination (Pontifex & Hillman 2007). More processing in frontal cortex counteracts the RAH theory (Dietrich & Audriffen 2011). However, especially due to reduced response accuracy/inhibition it might also be explained by an additional effort to recruit resources in the frontal lobe leading to neuroelectric inefficiency seen in an increased P3 amplitude (Pontifex & Hillman 2007). The decrease in N1 amplitude implies reduced visual attention whereas the increased P2 amplitude points towards better selective attention. However, global decreases in the N2 amplitude, whose wave has been suggested to originate from the ACC (van Veen & Carter 2002) might imply less conflict monitoring and more particularly less response

inhibition (Yeung et al. 2004; Pontifex & Hillman 2007) although reduced ACC activation has been associated with a reduction in response conflict and therefore increases in top down cognitive control (Carter et al. 2000). In other words, the smaller N2 amplitude during exercise might originate from an increased top-down control eliciting ACC deactivation, therefore leading to less conflict monitoring/impaired response inhibition, which is paired with a delay in cognitive processing speed related to response inhibition (Pontifex & Hillman 2007). On a behavioural level such a delay in overall cognitive processing was observed in the present study but not in their study. Unfortunately, specific reaction times for the inhibited responses were not analyzed in our study. Because subjects were supposed to inhibit their response for the incongruent trials (Pontifex & Hillman 2007), this finding is in line with our findings of increased commission errors and together, point towards selective exercise induced decrements in cognitive processing.

This is also supported by a cycling study of Davranche & McMorris (2009), which showed improvement in reaction time and cognitive adjustment during exercise but a more pronounced appearance of the so-called "Simon effect" that reflects an impaired ability to selectively inhibit an automatic response evidenced by delta plot analyses. They explained this effect with the activation-suppression model of Ridderinkhof (2002), stating a reduced interference effect for slower responses. It seems like the literature is rather consistent with an impairment of response inhibition due to acute exercise. According to Hershey et al. (2004) the frontal cortex is a main structure involved in inhibition of pre-planned responses and the particular brain circuits are innervated by dopamine, which is supported by the application of dopaminergic drugs exerting positive effects on response inhibition (Chamberlain et al. 2006). The link to exercise is given by Gerin & Privat (1998) showing increased cerebral concentrations of dopamine due to muscular and cardiorespiratory feedback, which might have an intensity dependent aspect as indicated by the results of the current study. Bilder et al. (2004) attribute the purpose of increases in tonic dopamine to maintenance of task rules and goals, which has been suggested to be a major contributor to the alertness for the unpredictable inhibitory signal and the speed at which pre-planned motor responses are aborted (Aron, Robbins & Poldrack 2004). In this light our results of increased commission errors during and after running could be partly due to increased dopamine affecting inhibitory networks leading to faster inhibitory responses, which cannot be inhibited possibly due to RAS-energized peripheral potentiation (Davranche et al. 2005) paired with blurry input computational output from the executive network. Unfortunately, reaction times for response inhibition errors were not analysed in the present study. However, response inhibition is only a part of executive control processes and future research is needed to examine a bigger picture not only of executive processes but also of the overall frontal cortex activity change in response to acute exercise because the current research mainly examines this relationship across a variety of cognitive measures that engage different frontal cortex functions. Furthermore, compared to a lot of choice reaction time task studies, which involved using both hands the present study only required one hand

innervation because bilateral simultaneous hand movement were shown to decrease the level of performance compared with unilateral hand movement, suggesting lower attention to each hand (Ohtsuki 1983).

Compared to the rather clear evidences of the effect of exercise on brain mechanisms involving explicit or implicit processing the effect of exercise on the combination of both is, however, rather unclear. Contrary to the results of the present study Pesce et al. (2003) found an improvement effect of reaction time in a global and local priming task during cycling at 60% VO_{2max} for 12min. Also during cycling, McMorris & Graydon (1997) found a facilitating effect on reaction time with no effect on accuracy in a quick decision making task, the second of which is in line with the finding of the present study. However, in both studies exercise consisted again of cycling whereas in this study running was used as exercise, which very likely demands more computational resources leading to an immediate impairment of performance, most likely due to an immediate shift (not transient) of activity away from the PFC. Even though meta-regression analysis (Labmourne & Tomporowski 2010) and meta-analysis (Chang et al. 2012) in the field of exercise and cognition involved 29 and 79 studies, respectively there is a very limited amount of studies investigating running effects on both, the explicit and the implicit information processing system. In the most recent one Dietrich & Sparling (2004) did not see an effect of 45min running at 75% HR_{max} on the Brief Kaufman Intelligence test. Moreover, in the same study but in a second experiment they found no effect of 65min running on the same intensity on the Peabody picture vocabulary test. However, they hypothesize that those two tests do not heavily depend on prefrontal cognition. In the same study they used the Wisconsin Card Sorting Test and the Paced Auditory serial addition task, which both are suggested to involve exclusively explicit processing and are suggested to be more dependent on prefrontal cognition. Both test performances were impaired during 45min and 65min of running at 75 HR_{max}. In contrast to a few studies trying to link neuroelectric and EEG measures to behavioural consequences of cognitive tests assessing executive function in response to exercise there is no literature investigating a link to executive measures involving a time component. This should be addressed in future studies.

The transient component of activity shift away from PFC domains (Dietrich 2003) in prolonged exercise bouts might be due to metabolic changes such as glycogen depletion in astrocytes (Matsui et al. 2012) and reduced influence of the RAS due to desensitized responses to the RAS after prolonged exercising. Another explanation might be a downregulated/impaired integration of sensory afferents due to hypofrontalility in the brain circuits responsible for afferent processing leading to a reduced trigger of the RAS and maybe delayed central fatigue. However, these are all hypotheses that remain to be shown and will be addressed in more detail further down.

4.1.2   Single Block analyses

Even though there is a clear immediate effect of exercise during running, the effect of intensity remained somewhat unclear (no posthoc differences between low and moderate intensity) and in addition to that it should also be taken into consideration that the CCPT test takes 14 minutes and is therefore not able to depict an instant reflection of brain activity but rather gives a summary over 14min, which suggested an immediate, impairing effect of exercise right at the onset of exercising, most likely due to the immediate, consistent computational demand of running that is not-changing as indicated by no dose (intensity) effect (in the implicit system) and therefore requires a shift of resources from the prefrontal networks involved in executive and attentional control to the primary motor cortex, secondary motor cortices (i.e. premotor and SMA), basal ganglia, the motor thalamus, cerebellum, red nucleus, substantia nigra, the massive pathway systems, and the motor neurons all along the spinal cord, among many others involving sensory motor integration (Dietrich 2003).

When looking at differences within the duration (14min) of the CCPT differences in intensity became clearer. The analysis of changes during the time course of 14min points towards an involvement of the reticular activating systems at beginning of running but only during low intensity running. It could be shown that on the one hand both, commission errors and reaction time during low intensity decreased from the first three blocks to the last three blocks at ISIs of 1sec, and 1 and 2sec, respectively whereas on the other hand, during moderate intensity, commission errors and reaction time increased from the first three blocks to the last three blocks at ISIs of 2 and 4sec, and 2sec, respectively. This in-depth analyses of single block values during the time course of running and the CCPT test (14min) add more details to the hypofrontality theory and imply a facilitating effect for both, reaction time and inhibitory control (commission errors) on low intensity exercising, most likely due to a involvement of the reticular-activating system (Dietrich 2011). This effect was then shown to be overwritten/overshadowed by moderate intensity running, which led to a increase in both, reaction time and commission errors, most likely due to a higher metabolic demand put up by a higher intensity, and not by higher computational challenges.

As suggested by the reaction time summary results of the 14min the computational demand is not likely to be very different in treadmill running on low and moderate intensity and may furthermore not change very much in prolonged treadmill running. Therefore we suggest that, in addition to the spatially localized challenges of running (termed "computational demand"), which immediately caused impaired performance on average when compared to baseline, the metabolic demand will further play a role in triggering a shift of activity away from the executive and attentional networks embedded in the prefrontal cortex by means of the running intensity, which therefore intensifies activity spatially in the already exercise-type-dependent active brain networks. Even though intensity effects have been detected before (Del Giorno et al. 2010) it has never been suggested that exercise

intensity stresses the activity/metabolic demand of neuronal networks encoding the mode of exercise in an intensity dependent fashion as the results of intensity-dependent impairment of response inhibition during running suggest. However, a very recent study was the first to actually give direct evidence for brain glycogen supercompensation in astrocytes following exhaustive exercise, which was correlated with the glycogen decrease during exercise (Matsui et al. 2012) showing that the extend of supercompensation was dependent on the glycogen decrease during exercise. The similarity of skeletal muscle and brain dynamics in these glycogen mechanisms lead therefore to the conclusion that higher intensities require higher turn-over rates of glycogen in the networks active and responsible for the type of movement. The threshold for this shift to become and stay evident in the cognitive measures of this study was between 40% and 60% VO_{2max} for a exercise bout of 14min but might be different for longer bouts of running since the energy supply might be limited in extreme cases or changes its energy transfer from the main metabolic resource to optimally supply the sustained metabolic needs and for trained people since they have optimized energy transfer system to satisfy a prolonged bout of exercise. In this regard enzyme activity level might explain the transient component of the cognitive decrease. Next to carbohydrate it has been repeatedly shown that neurons are also able to utilize lactic acid, produced by astrocytes, especially upon energy tightness (Suzuki et al. 2011). Since untrained people produce relatively more lactate that untrained, there might be a metabolic advantage for them. However, Hu & Wilson (1997) showed in a in vivo rat model that elevated lactic acid in the brain extracellular fluid could be depleted rapidly (up to 28%) in as little as 10-12sec of large neuronal activity. Instead, glutamate stimulated astrocytic glycolysis might account for neuronal substrate in longer activity. Since brain derived neurotrophic factors (BDNF) play a crucial role in cognitive performance it is worth mentioning that there is evidence that the BDNF response to exercise is not only dependent on the intensity protocol (Knaepen et al. 2010) but also on participant´s level of training (Castellano & White 2008; Zoladz et al. 2008). In more detail, higher intensity exercising leads to larger increase in BDNF and BDNF release is moderated in well-trained compared to less trained people, both evidences pointing towards a receptor desensitization.

Hence, in terms of metabolic supply athletes might achieve hypofrontality later because of larger glycogen stores. They might also stimulate the RAS less as a response to training (chronic adaptation) or have more desensitized receptors for its projections. Moreover, it should be considered that athletes are better able to oxidize fat. This might unbind tryptophan from its fatty acids and allow it to cross the blood brain barrier as a precursor for 5-HT. The computational demand is debatable, too. Athletes familiar with running would be expected to address a smaller amount of brain capacity to sustain running, which is evidenced by their economical running style. On the one side this would mean that they require higher metabolic demands to compensate for the reduced computational challenge in order to achieve a state of hypofrontality. On the other side, according to this rationale inexperienced runners would be expected to achieve a state of hypofrontality faster. However, a methodological

problem for the assessment of a hypofrontality state with cognitive tests is that with inexperienced runners there might be a dual task interference as a consequence of overloading the working memory. The present study involved young, healthy people that were familiar with treadmill running.

4.1.3   Interstimuli Interval comparison

Finally, it could be shown that reaction time increased linearly with the length of the ISI. This finding is in accordance with the findings of Epstein et al. (2006) who found a linear increase in the effect of medication on attention with the ISIs. Poorer performance during longer ISI Intervals is very likely related (Hee Hwang et al. 2010) to the cognitive energistic model (Sergeant 2000) according to which longer ISIs induce a low energetic state leading to slower and more inaccurate responses which in Epstein´s study (2010) could be normalized by medication. While the present study provided clear evidence for slower responses, for commission errors this normalization effect as indicated by a decrease in commission errors could in another study (Hee Hwang et al. 2010) only be shown for the 4sec ISI after transmagnetic stimulation (TMS) of the DLPFC. However, commission errors in the present study were only shown to be different for the 1, 2 and 4sec ISI during the first three blocks of low exercising and were highest in the 2sec ISI, which is supported by a similar trend at the last three blocks during moderate intensity running and by the above stated results for the single block analysis, which showed most significant changes in the 2sec ISI. Therefore we conclude that reaction time increases significantly with the length of the ISI whereas the explicit system shows its lowest energetic state in the 2sec ISI. However, because this could only be shown during low and moderate intensity running and not during the resting condition most failures of inhibitory control might only appear during running, implying that exercising might cause a shift in the before mentioned energistic model in the explicit system. Compared to other studies (Epstein et al. 2006; Hee Hwang et al. 2010) this study could show effects on all ISIs.

4.2   Discussion Post

4.2.1   CCPT Performance Variables

Five minutes after running, exercise had an intensity-dependent effect on reaction time, in a linear decreasing fashion with increasing intensity. Commission errors, however, showed a trend to increase in an intensity-dependent fashion. Moreover, response style was different after running indicating a more risky response style, particularly after low and high intensity running, pointing towards a more instinct-based behaviour. Perseveration errors, responses below the physiological possible 100ms threshold, were high after running compared to baseline. Also reaction time standard error block

change was higher after running. In addition, reaction time block change was increased after running, particularly after the high intensity interval session.

These findings of decreased processing time and increased inhibitory errors after running point towards intensity-dependent hypofrontality post exercising paired with an activity shift towards the implicit, bottom-up, information processing system at the cost of the ability the inhibit responses, which has never been explicitly looked at.

The literature on post running effects on cognition is relatively sparse. A study investigating the performance of a choice reaction time task showed decreased reaction times in very well trained triathletes after 100min on average which was only significant in the group that received CHO solution (Collardeau et al. 2001). The lack of finding a significant decrease in choice reaction time also in the placebo group is likely due to either too low intensity, which was ventilator threshold or the choice of well-trained athletes, who might have reduced response to afferent stimulated release of neuromodulators, similarly to what has been shown for BDNF (Zoladz et al. 2008; Knaepen et al. 2010).

Moreover, Themanson & Hillman (2006) conducted a study including 28 higher- and lower fit adults to investigate performance of a flanker task after 30min of treadmill running compared to resting. Although higher fit adults exhibited reduced error-related negativity (ERN) amplitude, increased error positive amplitude, and increased post error response slowing at rest compared to the lower fit adults, acute exercise influenced neither one of these measures nor response speed or accuracy. This lack of behavioural findings is likely due to poor methodological aspects of the study, involving a cross-sectional design and the lack of surveillance for heart rate adjustment to control for intensity. Especially the decreased ERN amplitude findings together with no behavioural change point towards an increased top-down control in higher fit adults paired with a task-related reduction in response conflict, leading to a decrease activation of the system (Themanson & Hillman 2006). This is in line with other findings of decreased ACC activation during cognitive flanker tasks in aerobically fit older adults (Colcombe et al. 2004) suggesting increased top-down attentional control (Carter et al. 2000), which might decrease activation through a concurrent reduction in behavioural conflict (Themanson & Hillman 2006). Post-error slowing and larger P_e amplitude observed in higher fit adults support this assumption. In this context our findings of reaction time slowing during the post running CCPT test might be interpreted as a behavioural indicator for higher recruitment and implementation of additional top-down attention to improve performance outcome. However, even though both, reaction time block change, and reaction time standard error block change showed higher values after running, not only the linear trend for intensity for this slowing, indicating other, possibly metabolic mechanisms but also the average worsening in response inhibition indicate the involvement of other,

possibly resource allocation mechanisms, rather than improved top-down attentional control. Still, the time course of response inhibition errors during the post running test remains to be shown.

Godefroy et al. (2002) tested six trained male triathletes with the critical flicker fusion (CFF) test before and immediately, 5, 20, 60min and one day after an incremental VO_{2max} test. While M_{tot} remained unchanged M_{di}, which was the difference between ascending and descending values, was decreased after the exercise but recovered after 1 day, indicating a transitory aspect of exercise-induced impairment. These results of a decreased flicker fusion threshold point towards a decrement in perceptual response after running exercise. However, it is arguable in what degree that test is dependent on prefrontal brain circuits and therefore comparisons to the results of the present study are difficult to make. Moreover, the incremental exercise to exhaustion used in the study of Godefroy et al. (2002) with individual differences in time to exhaustion that are dependent on their respective VO_{2max} values makes the results difficult to interpret.

With regards to executive control Del Giorno et al. (2010) found impairments in the CPT and WCST immediately after cycling for 30min at VT but not at 75% VT. This hint towards an intensity-dependent impairment is confirmed by the current findings of intensity-dependent increases in commission errors 5min post running. Interestingly, they found elevated perseverative errors in the WCST after cycling, similarly to the increase in perseverative errors 5min after running in this study. Preservative errors mirror the inability to inhibit a respond of a previously learned rule. This points towards the assumption that exercise impaired similar brain structures involved in response inhibition, embedded in the executive network. Moreover, our findings confirm the assumption of Del Giorno et al. (2010) that exercise related impairments of executive control remain elevated in an intensity-dependent fashion after exercise and there seems to be an intensity-threshold for these changes to become evident. The incorporation of three intensities in this study allows finer conclusions of post exercise results.

The present study showed slowing of reaction time during the test, which was particularly pronounced after high intensity training. However, the exact time effect information in the recovery period post exercise seems to differ in the literature. Kashihara & Nakahara (2005) found similarly to the results of the present study that vigorous exercise improved choice reaction time only for the first 8 minutes after exercise. Considering the 5 minutes rest before participants in the current study started the CCPT test, this finding is approximately in accordance with our results of reaction time block change, indicating that reaction time increased significantly throughout the 14 minutes of the test. Joyce et al. (2009) found faster reaction times after 30min of cycling at 40% maximal aerobic power similar to the decreased reaction time findings of the present study but this was not coincided with an accuracy change in the stop signals but instead with shorter stop-signal reaction times. This effect was

observable up to 52min after exercise cessation. Especially after HI exercise reaction time block change was different from baseline in the present study, which adds a timing effect to the potentiated implicit system. Even though reaction time standard error block change was shown to have low test-retest repeatability the fact that both, reaction time standard error, reaction time block change were significant point towards reaction time slowing during the test. These results suggest an impaired ability of adjusting responses to changing ISIs and therefore poorer vigilance after running, particularly after HI running. Some participants confirmed this was by judging their own performance as extraordinarily good during the first half of the test whereas the second half was perceived as "hard to concentrate". Thus, the faster reaction time achieved after HI exercise was very likely even better in the first half of the test whereas the second half was assumingly poor, leading to an averaged performance that was still better than in the other conditions. This might indicate different involvements of executive versus attentional networks and is shown in a study finding progressively decreased BOLD response during the CCPT task using fMRI (Tana et al. 2010). The fact that performance, as measured by reaction time, worsened throughout the test post running adds some timing information to the literature. It is not possible to estimate a specific point of time when performance started to get worse; rather a transient decrease took place. However, from the result variables it is not possible to say if the inhibitory control, as measured by commission errors recovered in an inverse fashion to reaction time. The behavioural finding implying hypofrontality in the highest cognitive centres paired with an decrease in reaction time after running points towards a more "instinct" behaviour of responding: Faster responses without the time adding function of higher order (more computational) processes. This is in line with the hypofrontality theory (Dietrich 2003) and makes sense from a evolutionary point of view when running requires fast reaction times to survive.

The intensity dependent decrease in reaction time might imply an intensity dependent triggering of the RAS by sensory afferent feedback during running whose neuromodulators are still circulating post exercise. Therefore the reported increase in reaction time throughout the CCPT test after running as indicated by reaction time block change might depict the disappearance of the neuromodulators due to their respective turnover rates. Adrenaline has been shown to have a half-life of 3 minutes and is reduced by 35% within 1 minute (Kjaer 1989). Since the time course of reaction time after 5 minutes of rest does not entirely fit the adrenaline fade there might also be metabolic recovery processes, such as glycogen supercompensation (Matsui et al. 2012) that were induced by the respective prior intensity. Hence that might explain the quick fade of facilitation in reaction time after high intensity running. Unfortunately, the CCPT test does not offer a variable that gives an insight about the course of inhibition errors. Single Block analyses might also serve that purpose in future studies using CCPT. As opposed to the during running condition in which the RAS likely "protected" reaction time from getting intensity-dependent impaired by the computation and metabolic challenge of running, in the post running condition the computational demand is gone and therefore the RAS can exert it´s

"rescuing" effect that now lead to even improved implicit processing without being covered up by a computational demand. However, there might still be metabolic recovery processes hindering the full effect and possibly impairing response inhibition, which is assumingly not facilitated by RAS. Interestingly, the bottom-up effect of the RAS seems again, like in the during condition, not to have any facilitating effect on the explicit information processing system, as mirrored by still impaired response inhibition. Instead, the highest cognitive centres are still impaired after running, in an intensity-dependent fashion, very likely due to metabolic recovery processes and resource allocation mechanisms. Metabolic recovery might be partly due to astrocytic glycogen supercompensation (Matsui et al. 2012), which involves energy-dependent transportation of glucose into those astrocytes that have been active and depleted in an intensity dependent fashion. This is mirrored by intensity dependent increase in inhibition errors post running and might be related to a potential intensity dependent depletion of brain glycogen stores during exercise.

The impairment effect of reaction time and response inhibition during running in the present study could simply be due to dual task interference of running and performing the CCPT test. However, cognitive tests (Kaufman Brief Intelligence Test and the Peabody Picture Vocabulary Test) that are not in the same degree dependent on prefrontal cortex function (Dietrich & Sparling 2004) as the ones stated did not get affected by exercise, what would be predicted according to a division of effort between exercise and a cognitive task. Nevertheless, a study investigating interference of a dual motor task on the M1 level showed that finger squeezing with 5% rather than 25% MVC and treadmill walking at 50% maximum walking speed (compared to 80% and 30%) decreases MEP, especially when the dual tasks are synchronized (Uehara et al. 2011). It is suggested that desynchronization of a dual motor task led to activation of secondary motor cortex such as SMA and premotor cortex, hence increasing M1 excitability (Uehara et al. 2011). In light of the present study these findings pose additional considerations regarding speed application and different clicking rhythms due to different ISI on the one hand but on the other hand give insight into brain pathways that might have to be regarded as single processing units. The projection from the PFC via the rIFC to the M1 might take a crucial role in initiating or inhibiting a motor response given differential M1 excitability depending on a "inner" frequency synchronization state between motor areas (given by the frequency of the exercise mode) and the top-down PFC part of clicking and inhibiting (ACC, rIFC and DLPFC). According to this assumption, in a M1-excited, desynchronized state, one would expect less response inhibition but quicker reaction times whereas a synchronized state would imply more accurate and slower responses. Especially, if the rIFC, next to the DLPFC and the ACC is the last chain of a brain network involved in response inhibition by directly or indirectly acting over motor areas (Aron & Poldrack 2004) a state of the whole PFC that is desynchronized with the supplementary motor area or the premotor cortex might let exercise-induced noisy output projections down from the DLPFC and ACC slip through and trigger a motor response that is not supposed to happen due to higher excitability in the motor areas.

Calculating both participants running and clicking frequency during different ISI could test this hypothesis by trying to relate that (de-) synchronization state to the hypothesized speed/accuracy trade-off in a desynchronized state.

The fact that a simple ratio calculation between commission errors and reaction time, hence normalizing response inhibition errors to the average reaction time leads to no difference of post running performance compared to the baseline ratio might point towards an activity balance of resources that got re-distributed towards the implicit system or a strategy shift. A speed-accuracy trade-off was also observed in a short memory task during cycling at 75% VO_{2max} (Adam et al. 1997). Moreover, participants statement of the perception of slow responses after running might lead to another explanation for faster reaction times that are perceived slower. The increase in commission errors is very likely due to less activity in executive brain networks, involving the DLPFC amongst others. The DLPFC was also shown to be involved in time perception (Harrington et al. 1998; Rao et al. 2001). Lesions in the right DLPFC could no longer discriminate intervals of 300 – 600 ms (Harrington et al. 1998) and imaging evidence showed right DLPFC activation in a temporal discrimination task in which 1 second intervals differed by 60-ms steps (Rao et al. 2001). Therefore reduction in DLPFC activity might also leads to a slowing in perception of time leading either directly to faster responses or indirectly to perception of slow responses, which are tried to be compensated for by the participants by reacting faster. Moreover, the cerocerebellum was hypothesized to be involved in time perception (Fierro et al. 2007). The implicit, bottom-up information processing pathway in which the cerebellum plays amongst others an important part was in this study shown to be improved in a intensity dependent manner after running. Based on this evidence one could argue that more activity in the cerebellum might have a negative link with time perception. However, this was not confirmed by Fierro et al. (2007) stating that "The right cerebellar rTMS worsened temporal discrimination of cutaneous somatosensory electrical stimuli on the ipsilateral hand". Since in the time perception studies the cerebellum seemed to be more relevant for discriminating time intervals well below 1sec whereas the DLPFC seems more crucial for longer interval discrimination it can be hypothesized that exercise had a stimulatory effect on the implicit system (cerebellum in particular) in an intensity dependent fashion but also to an impairment of DLPFC activity which might have led to an impaired temporal discrimination of the ISI which consisted of at least 1sec and consequently to a change in strategy leading to quicker responses in a intensity dependent fashion post exercise. Hence the increase in implicit information processing happens likely in combination with the decreased activity of the DLPFC due to hypofrontality, which was shown (Smith et al. 2003) to be also crucial for discrimination of time intervals of several hundred milliseconds where there is more load on the working memory and sustained attention.

Perseveration errors, or responses below 100ms, were influenced by exercise intensity in that they increased in a linear fashion with intensity with a little drop after high intensity. Nevertheless, none of the performances were different from each other. Response style was also shown to be affected by exercise intensity, with low and HI bringing the best performances. The increase in perseveration errors already after low intensity running points towards a disengagement of the DLPFC already after low intensity and long exercise bouts. Patients with lesions in the DLPFC were shown to have high numbers in perseverative errors in the WCST (Milner 1963) and a more recent factor analysis related to the WCST indicates than these perseverative errors might be the most useful measure assessing such cases (Greve et al. 2005). However, DLPFC lesion cases also show dysfunction in other executive functions. The fact that perseveration errors were not impaired in the during running condition might be due to the short (ca. 15min) time spent running compared to the post phase of the study participants ran at least 35min. Since intensities were the same this is likely not due to an intensity-dependent effect.

Even though not statistically significant, after HI running a drop in commission and perseveration errors could be observed. The 4x4 HI training consisted of changes between heart rates of 90% and 60% HR_{max}. This might have two opposing consequences. First, the change of intensity and therefore afferent trigger for the RAS does not allow neuromodulatory receptors to desensitize in a similar manner to chronic BDNF adaptations observed in higher fit people (Knaepen et al. 2010), possibly even leading to more quantity of RAS release. This might eventually enable neuromodulatory substances to diffuse to executive networks reducing commission and perseveration errors. Second, during the exhaustive intervals participants likely ran above their lactic threshold. Running above lactic threshold might likely impair running economy, reflected by a higher O_2 consumption than what running speed would predict. Consequently, poor running economy might lead to additional computational challenges next to the increased metabolic demand given by the higher intensity. Post running this computational challenge is gone and therefore the drop in perseveration and commission errors might reflect the additional RAS stimulation during high intensity training. This assumption is supported by McMorris (2009) suggesting that there is a projection of noradrenaline to the prefrontal cortex. Moreover, the threshold for noradrenaline release has been argued to be higher than adrenaline (McMorris 2009), which might explain the drop in commission and perseveration errors only after HI training. In addition, the present study also found a decrease in commission errors during low intensity running when analysing single blocks during running. This was only observable in the 2sec ISI condition, indicating that the effect might be not as strong. However, both, higher intensity, and more RAS stimulation (Brown 2004) are directly related to astrocytic glycogen depletion by increasing astrocytic glycogenolysis-enhancing factors, which leads to the conclusion that metabolic recovery processes in response to previous high intensity exercise are highest after HI interval training.

4.2.2   PANAS

Positive Affection was shown to increase after HI exercise, but no systematic association was observed changes in mood and cognitive performance. Although improvement of positive affection was not directly associated with performance measures, co-appearance of improved PA after running with the most hypofrontality state after HI Interval running but not after MI or LI might suggest a link between hypofrontality and mood that is only observable after HI, which was assumingly also the most hypofrontal state. A general improvement of mood after an acute single bout of exercise has been proposed (for a review see, Yeung 1996). A reduced negative mood, as assessed by POMS, was suggested to be associated with an increase in oxygenated hemoglobin (oxyHb) in the ventral PFC but not in the dorsal PFC during pedalling exercise (Fumoto et al. 2010). While negative affection is broadly correlated with symptoms and diagnosis of both anxiety and depression disorder, positive affection has been shown to be consistently, negatively related to diagnosis of depression only (Watson & Clark 1988). This indicates that in our study with participants running, the dorsal part of the PFC likely reduced activity as also evidenced by impaired response inhibition, especially after HI running, which similarly to the study of Fumoto et al. (2010) led to an enhanced mood.

Especially the left hemisphere has been associated with positive affection emotions in an EEG study (Harman & Ray 1977) as well as in a study assessing lateral eye ball movement in response to 60 reflective questions designed to manipulate affection (Ahern & Schwartz 1979). It is likely that the current study only found a difference in the positive affection scale and not in NA as in Fumoto et al. (2010) because the left DLPFC, which was suggested to have less activity after running as evidenced by preservative errors and response inhibition was by both, fMRI (Herrington et al. 2005) and EEG (Davidson 2004) studies shown to be activated by pleasant words, rather than negative ones. Particularly the left DLPFC seemed to account for lateralization effects found in EEG measures. However, Siegle et al. (2002) revealed longer processing of negative words in the amygdala, which was suggested to be related to decreased DLPFC activity leading to disinhibition of the amygdala (inverse functionality model). This would lead to hyperresponsivity of the limbic regions, such as the amygdala (Davidson et al. 2002). Pochon et al. (2002) have further hypothesized that limbic inhibition imposed by the DLPFC may serve to override top-down emotional control processes by selecting which representations to maintain. In other words, the limbic system influences choice (DLPFC) and the other way round. In conclusion, even though studies relate decrease activity of the DLPFC with an increase in bad mood, the current study found an increase in PA. This finding is in accordance with Hee Hwang et al. (2010) who found a negative effect on PA in the PANAS after a stimulatory protocol of rTMS on the DLPFC. Even though one might attribute that effect to the unpleasant physical sensation of the TMS stimulation, other studies (Mosimann et al. 2000; Vanderhasselt et al. 2007, 2009) revealed no changes in mood after a single session of high-frequency rTMS. However, the unspecific and rather global impairment of brain structures such as the VMPFC, DLPFC and the

ACC by exercise does not allow specific conclusions about the observed change in mood in the present study. Moreover, linking an increase in mood with a decrease in DLPFC activity does not make sense regarding current approaches of depression with stimulatory rTMS over the DLPFC because depression is associated with hypo-activity in the DLPFC (Mayberg et al. 1995). Instead, general decreased activity in the frontal cortex, especially with regards to the DLPFC could have simply led to a more out-balanced activity between the VMPFC and the DLPFC expressing itself in enhanced mood similar to what was observed in the study of Fumoto et al. (2010). Fumoto´s et al. (2010) finding of increased activity of the ventral PFC but not the dorsal PFC might mirror the ambivalent literature about effects of exercise on cognition because a lot of different tests are used that involve different brain structures. Considering RAS effects that have earlier been suggested to be associated with performance changes in the CCPT test during and after running exercise in the present study, the emotional change after running gets more complicated. The VMPFC has not only serotoninergic, inhibitory projections to the amygdala that lead to reduced emotional perceptions, but also dopaminergic, stimulatory projections that might have a motivational side to this emotional element of action decision making.

A major limitation is that the PANAS mood score was not translated into Norwegian and since all participants were Norwegian citizens the exact understanding of single words might have been a problem. Taken together, improved PA after HI suggests 1) a activity decrease in PFC 2) that the hypo state is able to explain mood changes, possibly by decreasing activity in amygdala, either directly or via PFC projections.

4.3   Discussion Gender, Age and VO_{2max} effects

Adjusting variables that were significant in the during and post running conditions to gender, age and VO_{2max} indicated a trend that processing time (RT) at baseline had a tendency to be increased in the older population and differently affected by exercise intensity. More specifically, reaction times of the higher age group, defined as the late twenties stayed relatively the same on the different intensities whereas the younger group, defined as the early twenties, seemed to be more impaired by intensity but still performed on average faster than the older group. Moreover, increases in reaction time during the test as indicated by reaction time block change post running were also more stable over intensities but higher in the older group.

Baseline increases in RT with age after the age of 18 have been documented before (Strauss, Sherman & Streen 1998, p. 566) but never in connection with acute exercise on different intensities. Because all participants were very active people the fact that age got less affected by intensity might mirror chronic adaptations in the older group such that a possibly advantageous earlier stage of

hypofrontality, as seen in increased reaction time, is achieved faster. Another explanation might be a desensitization of neuromodulator receptors involved in circuits making up the implicit processing system (RT).

Grouping for VO_{2max} confirms the first idea by giving indications for chronic adaptations mirrored by the higher VO_{2max} group: Even though performance as measured by commission errors was similar at baseline, there was a strong trend for the high VO_{2max} group to be less affected by exercise intensity compared to the less trained people possibly indicating chronic adaptations that lead to an earlier state of hypofrontality, which might be advantageous for exercise performance as will be discussed in chapter 4.4. Reaction time increase but not response inhibition has previously been shown to be attenuated by subjects with higher VO_{2max} values during exhaustive cycling exercise (Ando et al. 2005). A more effective oxygen supply given by higher maximal aerobic capacity to brain regions active during exhaustive exercise could result in augmented oxygen availability for cerebral metabolism (Dustman et al. 1994).

In terms of reaction time chronic adaptations to exercise can be derived from a study finding faster reaction time in college students who play basketball compared to sedentary students (Nakamoto & Mori 2008). Moreover, the greater the sport experience, the faster were the reaction times in response to baseball-specific stimuli.

Nevertheless, commission errors have also been hypothesized to be affected by gender (Burton et al. 2009). In this study commission errors were also differently affected by exercise intensity in male and female but were not different at baseline. In addition, reaction time standard error block change post running was differently affected by exercise intensity in males and females. More specifically the results indicate that males were less affected by exercise intensity than females, which might be due to a gender effect. In contrast, Yagi et al. (1999) were not able to produce a gender effect on the exercise-cognition interaction.

However, there are two limitations to be considered. First, grouping participants leads to very small group sizes, which results in low power and analysis of gender, age or VO_{2max} effects are beyond the scope of the present study. Second, it is not possible to distinguish if differences are due to gender or VO_{2max} because the female group was also the group with low VO_{2max} values. Moreover, the floor effect (Themanson & Hillman 2006) may imply interferences of age and VO_{2max}. That is, fitness is related to shorter reaction times in tasks requiring more top-down attentional control in older but no younger adults. Still, the subjects of the present study did not include older participants than age 35.

4.4   Discussion TMS & tDCS

Lots of evidence from the result of the present study is pointing towards DLPFC disengagement: worsening in response inhibition, perseverative errors, and the concept of delayed time perception. The mood increase, however, is more difficult to explain because in depression, stimulatory TMS protocols are used to increase DLPFC activity, which is suggested to show hypo-activity in depression. Therefore, we sought to investigate if a simulated DLPFC lesion is sufficient to explain our results and might serve as an evidence for the RAH theory. Moreover, a potential association between hypofrontality and central fatigue was investigated. To simulate a state of hypofrontality and to investigate which brain regions might be involved in the executive control function of the CCPT test the second experiment involving tDCS and TMS was carried out in collaboration with the Sobell Department of Motor Neuroscience and Movement Disorders at University College London (UCL).

Two studies that used the CCPT test point towards the DLPFC and the ACC as the main regions active during the administration of the CCPT. Using fMRI Tana et al. (2010) show an extensive brain network activated, including frontal, temporal, and occipital cortical areas as well as left cerebellum. In terms of volume extend and magnitude the frontal region with the rACC sticked out, reflecting its involvement in a sustained attentional network. Interestingly, the BOLD response decreased throughout the test without any deterioration in performance suggesting more efficient processing and increased top-down control (Colcombe et al. 2004; Carter et al. 2000). However, Tana et al. (2010) attribute this raise and subsequent decrease to a mismatch between augmented regional cerebral blood flow (rCBF) requested by brain activity and augmented oxygen consumption resulting in a initial decrease of deoxy-Hb (increase in BOLD) that is followed by a restoration of the equilibrium between cerebral blood flow and oxidative metabolism. Activation in the left occipital and temporal cortex was located in the ventral visual pathway pointing towards letter recognition. The other study (Hee Hwang et al. 2010) used rTMS to stimulate the DLPFC and found a decrease in commission errors, similarly to our findings but only in the 4sec ISI, which was attributed to the before mentioned lower cortical state after a longer delay period. However, one major limitation of that study, which might also have affected the results of the present study, is that stimulation intensity of 90% of motor threshold with a frequency of 10 Hz has been demonstrated to reliably change neuromodulation of prefrontal and striatal regions (Barrett et al. 2004; Sibon et al. 2007). Especially the modulation of striatal regions might influence neurotransmitter release and therefore the distinction whether RAS effects or TMS effects modulating activity of the DLPFC is difficult to make.

Nevertheless, these findings points towards the DLPFC as a potential brain structure involved in response inhibition whereas the ACC was hypothesized to be crucial for sustained attention involving error detection and performance monitoring (Tana et al. 2010; Aron, Robbins & Poldrack 2004) and the inferior frontal cortex (IFC) or more specifically the rIFC might be involved in the final

suppression of an action by impacting either subcortically over the subthalamic nucleus (STN) or the brainstem or the motor cortex (Aron, Robbins & Poldrack 2004). However, there is also evidence from multichannel functional near-infrared-spectroscopy (fNIRS) that during 50% VO_{2peak} cycling an improvement in reaction time in the Stroop interference test is due to enhanced DLPFC activation (Yanagisawa et al. 2010). Our findings of decreased reaction times and increased commission errors during cathodal tDCS at rest rather point towards a disengagement of the DLPFC after running because the post running effects showed a similar performance pattern as the simulation of a DLPFC lesion. Stimulation the DLPFC with cTBS further decreased reaction time and increased commission errors compared to cathodal tDCS at rest or post running alone. Therefore, the present study concludes that cTBS is a better method to decrease frontal cortex activity compared to tDCS and moreover, might also be more accurate for stimulating the desired brain area. The fact the anodal tDCS could not completely restore the baseline values after running indicates that exercise has a very potent effect on frontal brain regions. However, during running effects could not be reproduced pointing towards different mechanisms such as computational and metabolic requirements, active during exercise and recovery.

Interestingly, studies that indicate a link between central fatigue and motor cortex excitability by showing reduced MEP after a treadmill marathon run (Ross et al. 2007) or already after finger tapping (Yahagi et al. 2005) might serve as an explanatory basis for a potential association between a state of hypofrontality and central fatigue. Both phenomena are triggered by afferent feedback from muscles that activate the RAS. Brain monoamines, such as noradrenaline and 5-hydroxytryptamine elicit a decrease in brain glycogen in response to prolonged exhaustive exercise with hypo-glycaemia and are therefore not only inducing factors for central fatigue (Newsholme et al. 1992) but also glycogenolysis-enhancing factors in astrocytes (Brown 2004). Hence, brain glycogen may be the direct link to a continuum at whose ends is a state of hypofrontality and central fatigue. This leads to several possible hypothesis that were attempted to address with the data presented in this study. Our findings of increased motor evoked potentials (MEP) after a short bout of exercise suggests elevated motor cortex excitability. In this light, faster reaction times that were found post running could be due to a higher excitability state of the motor cortex rather than, or in addition to the suggested peripheral facilitation effect of arousing neurotransmitters (Davranche et al. 2005). Moreover, in the same post exercise periods subjects were shown to have impaired inhibitory function and decreased reaction times, suggesting a state of hypofrontality. This might point towards an advantageous state of hypofrontality to drive motor functions. Since central fatigue has been observed after running (Ross et al. 2007) and our findings show increased M1 excitability after running, similarly to increased brain activity in motor areas in MS patients suffering from central fatigue, there might be an association between this two phenomena. However, our findings are in contrast to the findings of Ross et al. (2007) who found decreased MEP after treadmill marathon running. The different findings are likely

due to the length of running. In the present study subjects only ran for 35 minutes, which might represent an initial state of hypofrontality that could even serve to purpose to enhance performance. It is therefore possible that the increased excitability of the motor cortex reflects an activity shift of resources to motor areas, causing a state of hypofrontality and an elevated activity in motor areas. After a very long run even the motor cortex seems to reduce excitability. Interestingly, both, hypofrontality and central fatigue have been suggested to happen because of a widespread activity pattern in the brain, either due to computational challenges or dysfunction from an unknown cause implying that these two states are linked and therefore allowing further investigations to compare them in health and disease (see chapter 1.4). Looking at the whole picture this might indicate the complexity of symptoms reaching from depression to multiple sclerosis. A common trigger for both, hypofrontality and central fatigue seems afferent feedback integration, which activates the RAS. RAS activation on the other hand has been argued to play an important trigger for central fatigue (Newsholme et al. 1992) as well as glycogenolysis-enhancing factors in astrocytes. Consequently, glycogen stores in the brain are depleted faster, which in this study has been argued to be a potential cause for hypofrontality as a shift of metabolic resources is required. Hence, central fatigue and a state of hypofrontality might go hand in hand. The findings of decreased MEP after marathon running (Ross et al. 2007) could be a result of hypofrontality, reducing activity in afferent sensory-motor integration centres, reducing the feedback-driven trigger of RAS and hence could delay central fatigue. These assumptions are hypothetical and should be addressed in future work.

Interestingly, preliminary data that was not presented in the result section showed increased MEP in M1 after inhibitory cTBS stimulation of the DLPFC. This might indicate a direct link between hypofrontality and central fatigue and more particularly could point towards an advantage to have hypometabolism in frontal regions in order to optimally drive motor processes during the initial phase of exercise.

4.5   Study Limitations

The present study has several limitations that need to be considered. In terms of the study design running for only 15 minutes could be argued to be too short to see differences in cognitive performance but turned out to be enough and thus suggests additional computational challenges for running compared to cycling. Even though some people might argue that the combination of running with cognitive tests might not have been the best choice to investigate exercise effects this turned out to be a strength of the study and allowed to add important findings to the literature. Running is also the most freely available exercise mode and is particularly important to research for implications in working places demanding physical activity. Moreover, intensity was controlled by heart rate and therefore the different computational challenges of running on different incline positions were not

taken into consideration. Furthermore, in the post running condition time effects for reaction time could be added but not for the response inhibition performance. The commercially available CCPT test does not give variables that indicate the course of inhibitory control throughout the 14min of the test administration.

Instead, single block values could have been calculated and compared (like in the during condition). Even though a training effect of other cognitive tests has been suggested before, the CCPT test was shown to be reliable (Chen et al. 2009). Also the analyses of the single block values revealed no significant difference between the first three blocks and the last three blocks of the test at baseline. Increases in reaction time during running were hypothesized to be an effect of altered cerebral blood flow or to be a cause of brain neurotransmitter, such as catecholamines and/or endorphins. However, the actual mechanism that would support a functional link between exercise and suggested theories of cognitive modulation remain to be established. The current study only provides evidence on a behavioural level. Hence, since no cerebral blood flow measures or blood probes to detect neurotransmitter were taken, our results are limited to only show indirect evidence for these hypotheses. Complementary methods in further experiments are necessary to validate our assumptions and interpretation of results.

Another issue in the current study is given by the tread-off between time and intensity. While the not energy matched low and moderate exercise conditions during running allow direct comparison of intensity effects because there was no time effect, the post running design was energetically matched and makes it therefore harder to distinguish if metabolic factors were more stressed through time or intensity dependency. However, this design allowed the conclusion that both, time and intensity interact in an additional manner. One more aspect that should be taken into consideration is the high probability of a self-selection effect of the participants, which is mirrored by the high VO_{2max} average values. Studies that involve exercise and the opportunity to perform a VO_{2max} test might particularly attract active people.

Last, the results of gender, age and VO_{2max} effects should be interpreted carefully because it was not the main scope of the present study to investigate those effects and group sizes restrict power of these analyses. However, for the data presentation regression plots would have been better to illustrate the data.

4.6   Clinical Implications

These findings have implications for all sorts of branches including, fire-fighters, policemen, and athletes and most importantly for treating clinical conditions such as obsessive compulsive disorder

(OCD), depression, posttraumatic stress disorder, phobia and anxiety disorders. These diseases all have hyperactivity in either the amygdala or the PFC in common. The VMPFC is not only involved in complex emotions but for OCD patients it could be shown that there is a hypermetabolism in that structure (Baxter 1990; Baxter et al. 1987). Also for post traumatic stress disorder and phobia a hyperactivity in the amygdala (LeDoux 1996) has been proposed leading to hyper-vigilance and hyper-awareness of reinforcing circuits leading to focusing on anxiety. In depression PET studies indicate a similar picture of hyperactivity in both, the VMPFC and the amygdala (Mayberg 1997; Mayberg et al. 1995), which might explain the frequent co-occurrence of both diseases. However, the matter complicates with a simultaneous hypoactivity in the DLPFC in depression, depriving the patients of the higher cognitive function that would attenuate and reason the negative mood. Therefore an abnormal interaction between VMPFC and DLPFC is suggested rather than global inactivity of the PFC (Starkstein & Robinson 1999). A shift of activity away from the VMPFC as a response to pedalling exercise (Fumoto et al. 2010) was associated with reduction in negative mood and the present study adds evidence of an intensity dependent shift away from the PFC or more particularly from the executive control network of the explicit information processing system. This was associated with an increase in positive affection after HI running. The current study reveals that longer and more intense running leads to a more pronounced hypofrontality state that might help in re-establishing a normal activity pattern in the PFC in the mentioned diseases.

Although Dietrich (2003) argues that observable effects of a hypofrontal state are only recognizable in a behavioural assessment after an extremely long exercise bout below lactic threshold because intensities above threshold could not be sustained for long enough, the present findings suggest that an exercise mode with high computational challenges that optimally involves balance and sensory feedback and consists of high intensities above threshold paired with recovery periods leads to cognitive performances indicating hypofrontality in as little as 35min. The Trondheim 4x4 high intensity interval paradigm used in this study led to improved PA indicating decreased activity in the PFC (Fumoto et al. 2010), lowest reaction times, impaired response inhibition and perseveration errors again, indicating decreased DLPFC activity and hence hypofrontality. Next to the higher metabolic stress given by higher intensity (above threshold), which also leads to more glycogen usage and therefore less availability for the brain, the high intensity interval training has the advantage of running above the lactic threshold which impairs running economy, as evidenced by a sudden, unproportional rise of VO above threshold, eventually leading to a higher computational challenge. Furthermore, uphill running might induce and additional computational challenge.

This study also shows that athletes need longer processing time during exercise but still make more mistakes in responses to stimuli that are supposed to be inhibited. Since especially inhibitory errors were intensity dependent impaired it would make sense for professional athletes such as football

players to higher their VO$_{2max}$ so that when they compete they perform at lower relative levels and therefore are less susceptible to pass the ball even though the situation changes in the last second so that the pass would lead to a fail pass.

Even though the current study considered particularly inhibitory control as part of the explicit processing system information being impaired during and after exercise a general reduction in the explicit information processing pathways would imply two aspects for tennis players. First, playing at higher intensities would not only lead to more inhibitory errors but also to less "thinking" about errors in general, possibly leading to better performance by a more automatized motor outcome. Consequently, evidence for hypofrontality during exercise might have implications and add a new rationale to warming up, particularly in sports that require a high degree intrinsic control as in tennis because a proper warm-up protocol might disinhibit intrinsic information processing from explicit and thus increase performance (Dietrich 2003). According to the results of this study warming up should be performed at rather high intensities for a longer time. However, secondly, reduction of activity in the explicit system does not overload its capacity and could therefore reduce learning effects.

Finally, in contrast to team sports, for endurance sports a reduction in PFC activity might be beneficial and even explain the state of "flow" and "runner´s high" (Dietrich 2004). Since brain resources in a prolonged endurance competition are allocated in other areas than the PFC and amygdala the athletes are likely to run without thinking and emotions, which might boost their performance. Another explanation might lie in a continuum of hypofrontality at whose end is central fatigue. Our findings indicate that short-term exercise potentiates the primary motor cortex and together with another study finding decreased motor cortex excitability after a marathon run (Ross et al. 2007) this suggests that hypofrontality co-appears with central fatigue. According to this assumption, increasing glycogen stores in the brain with exercise (Matsui et al. 2012) might serve to sustain central command from the M1 to the muscles, delaying central fatigue. Increasing glycogen under normoglycaemic conditions with the glycogen phosphorylase inhibitor (CP-316,819) that still allows glycogen utilization under hypoglycaemic conditions was shown to increase neuronal activation tine in the cortex during hypoglycaemia (Suh et al. 2007). However, the mechanisms are yet unclear and the end of the arrow from central fatigue to hypofrontality or the other way round is questionable. Afferent feedback has been shown to be a common initiator or modulator of both, central fatigue (Newsholme et al. 1998) and RAS (McMorris 2009). Our pilot data might also imply a direct pathway from the DLPFC to M1 by showing elevated MEP after cTBS of the DLPFC. Simulating a hypofrontal state of the DLPFC might imply impaired sensory afferent integration (possibly by the DLPFC), leading to delayed central fatigue and elevated M1 output. However, our finding might also just be an indicator of successful DLPFC stimulation. Therefore a distinction line is difficult to draw and should be addressed in future studies.

4.7   Suggested Model for Exercise Effect on Cognitive Function

Our study adds to a growing body of literature regarding the systematic assessment of a dose effect and effect time information. Both 40% and 60% VO_{2max} running triggered hypofrontality with the potential arousing RAS effects being covered up in-between those intensities. Executive control is impaired in an intensity dependent fashion. 5 minutes post running the reaction time was not only recovered but even faster than baseline in an intensity dependent fashion. However, 12 minutes after running the facilitating effect on reaction time seems to fade in an intensity dependent fashion. Moreover, so far no one has assessed effects of exercise on attentional and executive control with a well-recognized and established neuropsychological test in the field of psychology. This test combines simple reaction time task that challenge the implicit system and require constant attention (opposed to traditional CPT tests) with the executive system by means of inhibitory control, hence creating a more realistic simulation of real life events. Together, this combination might involve different or additional brain circuits than their single parts of reaction and higher cognitive centres. Furthermore, the literature lacks a study that compares the effect of different intensities that are energetically matched.

Based on the result of the present study we suggest a model for the effect of exercise intensity on cognitive function. Right from the first minute of running there is a computational demand mirrored by localized active areas in the brain that do not spatially change activity with intensity and hence running speed. This leads to hypofrontality indicating a stronger computational effect than the bottom-up, arousal effect of the RAS can exert on the implicit information processing system (RT). Intensity adds to this shift of resources by stressing the metabolic system of the neurons active in those areas specific for the type of exercise mode performed. Consequently, exercise duration exerts its effects rather through metabolic pathways than computational challenges. However, computational and metabolic demands are not uncoupled, but rather the computational challenge leads to allocation of metabolic resources. Therefore the metabolic demand that is also there from the first minute of exercising is intensity dependent and ads up to triggering hypofrontality by intensifying activity. This study could show that summarizing 14 min of running the computational demand was on average enough to trigger hypofrontality from which the pivotal implicit processing system got sort of "protected" from further impairments (hence not intensity dependent), most likely due to either direct RAS projections to the basal ganglia, cerebellum and supplementary motor area or to the quantity of RAS released neuromodulator-specific receptors in those areas. In contrast, the highest order explicit information processing system showed intensity dependent impairment (no bottom-up RAS rescue) in its response inhibition function because the brain circuits involved in executive control are not essential for running and its higher computational power would instead, even prolong processing time.

However, within those 14 min of running it seemed like low intensity and therefore low metabolic demand was not enough to cover up the activating effects of the reticular system whereas moderate

intensity and therefore a higher metabolic stress for the neurons supported the decrease in PFC networks involved in executive function, which could not be recovered by RAS. Hence, the transient decrease during steady intensity is due to metabolic exhaustion and changes to slower energy transfer mechanisms (more fat because low glucose availability). On the other side decrease of the RAS effects in prolonged exercise bouts should be considered, especially with regard to either desensitization/reduced neurotransmitter release, or hypofrontality leading to an impaired integration of sensory afferents that are responsible for triggering the RAS.
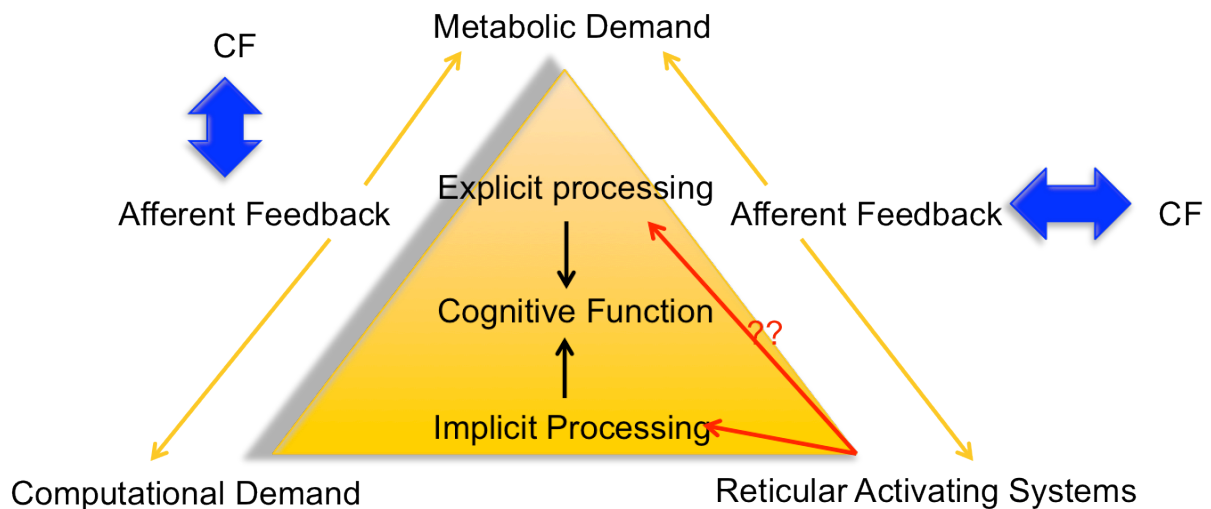

Figure 41: Model of Cognitive Function during Exercise
Note. The pyramid indicates that cognitive performance is influenced by the computational demand of the exercise, the metabolic demand and the activation of the reticular system. Moreover, explicit and implicit information processing, which influences cognitive function are differently affected by exercise and particularly by the reticular activating system. As these processes are greatly controlled by afferent feedback, there might be a crosslink to central fatigue. CF: Central Fatigue.

After running the higher cognitive centres, in which the executive system is embedded are still in a hypofrontal state as indicated by poorer inhibitory control. This might be due to metabolic recovery processes involving glycogen supercompensation (Matsui et al. 2012) and/or replenishment of the extracellular lactic acid pool (Hu & Wilson 1997), which requires energy. However, there is an intensity dependent increase in activity in the implicit information processing system leading to faster reaction times. This pivotal implicit function for surviving by reacting fast, without the time-adding higher function and computation processes of the explicit system, are now observable because first, there is no more computational demand and second, the RAS can exert its bottom-up, facilitatory effects on the implicit system. Paired with reduced activity in the explicit system this leads to decreases in reaction time that might be vital for surviving. However, after afferent sensory feedback of running triggered release of the neuromodulators and they circulate in the body they have a relatively fast turnover rate and their facilitating effect on the implicit system fades, as indicated by slowing of reaction time already within the 14min duration of the CCPT test. In addition, metabolic recovery normalizes and brain activity goes back to a homeostasis.
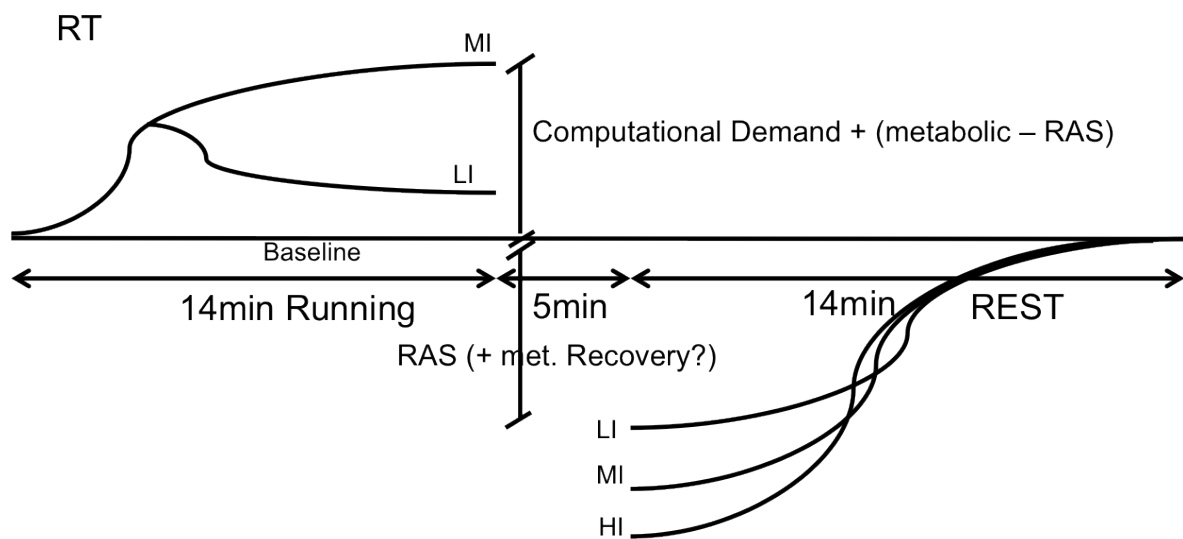
Figure 42: Effect Time information of the intrinsic information processing system
Note. The intrinsic information processing system as represented by reaction time in the present study was shown to be impaired during 14 minutes of running, likely due to a high computational demand of running. However, on low intensity facilitation on reaction was observed pointing towards an arousal effect shining through. Moderate intensity further increased reaction time as a result of higher intensity stressing the metabolic system of the active neurons more and therefore covers up reticular activating effects. After 5 minutes of rest reaction time was observed to be decreased in a linear, intensity dependent fashion. As the computational demand is gone this likely due to the arousing effect of the reticular activating system. The increase in reaction time back to resting values seems to be accelerated after high intensity training, pointing towards a potential involvement of metabolic recovery processes in prior active neurons. RAS: reticular activating system; LI: low intensity; MI: moderate intensity; HI: high intensity.
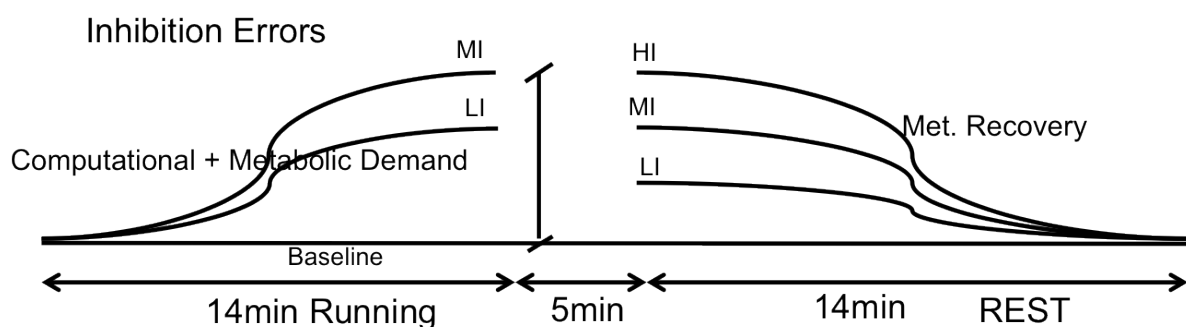
Figure 43: Effect Time Information of the extrinsic, inhibitory information processing system
Note. The explicit information processing system as represented by inhibition errors in the present study was shown to be impaired during 14 minutes of running, likely due to a high computational demand of running. The intensity dependency points towards a metabolic involvement given by intensity. After 5 minutes of rest inhibition errors were observed to be increased in a linear, intensity dependent fashion, again implying that the metabolic system was stressed in those parts of the brain that were required for running. Worsening in inhibitory control might imply a state of hypofrontality and might indicate that there is no arousing projection from the reticular activating system to the executive network. RAS: reticular activating system; LI: low intensity; MI: moderate intensity; HI: high intensity.

With the start of running exercise the primary motor cortex experiences a rise in activity and excitability. However, in longer exercise bouts with prolonged firing of afferent feedback, glycogen stores in specific brain areas deplete and not only further pronounce the hypofrontal state but also depress the drive of the primary motor cortex to activate muscles peripherally. There might be a direct, inverse link of activity decrease in the DLPFC and excitability of M1. In terms of physical performance such a link would imply that a hypofrontal state would be advantageous to drive motor processes. However, when brain glycogen stores deplete motor excitability decreases and the hypofrontal state results in behaviour similarly to that observed in frontal lobe lesion patients.

In summary, we show that acute exercise impairs cognitive function in a somewhat task-specific manner. Reaction time got impaired during running but is recovered and even improved after exercise in an intensity-dependent fashion. These findings may increase our understandings of shifts in specific activity patterns and eventually contribute to involve exercise as a treatment in diseases with a dysbalance in activity of brain circuits embedded in the prefrontal cortex.

5   Conclusion

The main findings of the current study was an increase in reaction time paired with a non-significant intensity-dependent increase in inhibitory errors during running on the one hand and an intensity-dependent decrease in reaction time that was also accompanied by an intensity-dependent increase in inhibitory errors after running on the other hand. The differences in findings during-exercise and after-exercise suggests contributing mechanisms such as computational and metabolic factors may be differentially active at different time points during exercise and recovery. More precisely, the computational demand was suggested to be negligibly different on different running speeds but was on average, enough to impair performance accordingly to a state of hypofrontality. The metabolic demand was further suggested to add up to this process in an intensity-dependent fashion and was suggested to cover up activating effects of the reticular formation that act via different neurotransmitter systems if intensity is high enough. Moreover, the inverse and selective dependency of intensity on reaction time during exercise and recovery implies that RAS activity is linearly dependent on exercise intensity, but that its effect may be obscured by accompanying, superimposed processes. The selectivity is likely due to different projections to different brain circuits/networks. Rather than general conclusions about exercise effects on cognition this study provides evidence for selective impairment of response inhibition, which also seemed less influenced by RAS compared to reaction time. We sum up:

> ➢ Exercise induces a state of hypofrontality, which lasts into the post exercise state, is affected by intensity and exerts different effects on brain circuits involved in implicit and extrinsic information processing.

> ➢ Exercise Intensity exerts its effect most likely through metabolic demands in neurons that are active and together, build the computational network for the type of movement involved.

> ➢ We add dose dependency and effect timing information to the literature. Moreover, the results support the RAH model (Dietrich & Audriffen 2011) but add details to it.

Reducing activity in the left PFC with cathodal tDCS was not as strong as but had similar effects as the post running results supporting the notion of reduced frontal activity post running. This was underlined and pronounced by an inhibitory cTBS protocol over the left DLPFC. However, the use of anodal tDCS to increase frontal lobe activity in the immediate post exercise period was unable to modify the post exercise effects, supporting the view that different factors may operate to produce the during and post exercise effects and pointing towards robust and strong exercise effects. Reaction time slowing during running could not be mimicked and might be due to either a higher computational demand of running leading to a disengagement, reflecting a decreased PFC metabolism or less likely due to dual task interference. The increase in inhibitory errors post running might be partly due to

metabolic recovery processes and are paired with instinctively, very fast reactions. The first mentioned effect is present even after exercise. At this point there is no longer the additional computational demand but there may still be metabolic recovery processes going on and there are might not be a rescuing, bottom up projection of the arousal system if intensity is too low. Enhanced motor cortex excitability after a short bout of exercise paired with hypofrontal behavioural indices suggests an advantageous hypofrontal state to drive motor processes during early stages of running. Further research should look into an association between central fatigue and hypofrontality by investigating connections between structures in the PFC and motor areas and should also focus on afferent feedback, which seems the trigger for a lot of connecting processes.

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Appendix A – Participation Poster
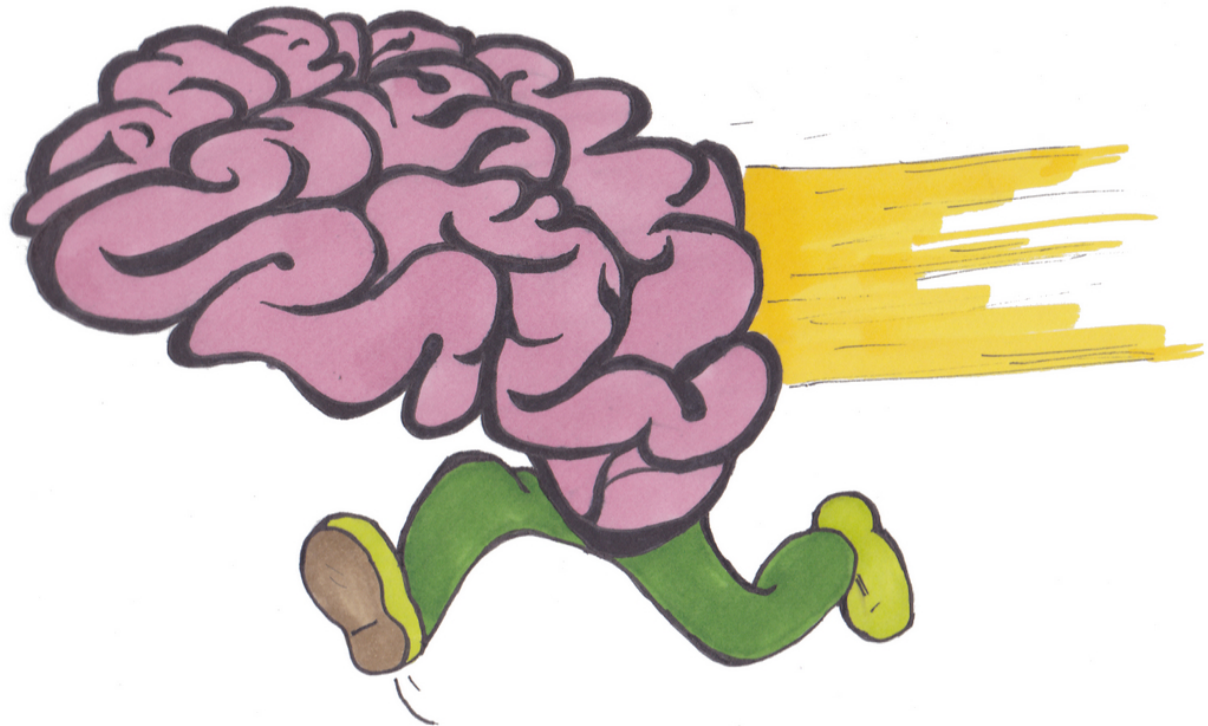
Would you like to participate in a research study investigating training intensity, mood and brain function in the frontal lobe?

We are looking for healthy volunteers aged 18-35 with no history of heart conditions or brain disorders (neurological or psychiatric).

The study will involve some initial testing including a VO_{2max} test, followed by five exercise sessions. Participating in the study will involve 6 visits to our lab at St. Olav's Hospital in total during the autumn.

We are looking for people who are able to maintain a fairly regular sleep pattern while they are participating in the study.

For more information please contact Martin:

wohlwend@stud.ntnu.no

Appendix B – Consent Form

REQUEST TO PARTICIPATE IN A SCIENTIFIC INVESTIGATION

The effect of exercise intensity on executive function and mood

You have been asked to take part in an experiment at the Institute for Circulation and Medical imaging, the Medical Faculty, NTNU. The experiment is the Masters-thesis project of Martin Wohlwend. The project is led by Dr Helen S. Palmer, post doctoral researcher (MI lab, fMRI group) with supervision by Dr Asta Håberg and in collaboration with Professor Ulrik Wisløff's group.

It is important that you read the following information before you decide whether or not to give your consent to participate in the study. Please ask questions if there is anything you are unsure about.

1. Background and general aims

Due to the computational challenges of movement, exercise affects local brain metabolism. This study will investigate whether changes in regional activity levels in the brain affect attention and mood. We are particularly interested in investigating how the brain is affected differently by different exercise intensities.

2. What will happen?

The experiment will take place at "Treningsenhet 1" at AHL at St. Olavs Hospital. During the familiarisation session you will take the Connors Continuous Performance test (CCPT). Then if you choose to participate in the study there will be six further sessions. At the next session you will take the CCPT again and also undertake a VO2 max test on the treadmill as a test of your fitness/ condition. At the final 5 appointments you will be asked to perform a combination of treadmill exercise (20-70 min exercise) and one CCPT test, sometimes during exercise and sometimes after exercise. You will also be asked to complete short questionnaires related to your emotions at some of the appointments.

3. Who can take part?

Subjects are healthy men and women aged 18-35 years old. Only people with no history of heart conditions or brain disorders (neurological or psychiatric) can participate. Participation is not possible if your are pregnant. Subjects will primarily be recruited from NTNU's students. In total 30 people will participate in the study.

4. Risk/ discomfort

For healthy individuals there is no known risk of treadmill exercise, CCPT tests or mood questionnaires. However, the high intensity exercise which you will experience during the VO2 max test and high intensity exercise session may provide some discomfort.

5. Volunteering

We would like to underline the fact that participation is voluntary. You are able to withdraw from the study at any point without giving a reason.

6. Timeframe

This study will take place in Autumn 2011. If you choose to participate we would like you to attend 7 sessions in total during autumn 2011, including this familiarisation session.

7. Data and confidentiality

All data will be handled confidentially. After data collection is complete (December 2011) the data will be made anonymous. After the data had been analysed and approximately two years after the study has been written up all the original data will be destroyed/ deleted.

8. Economy / compensation

The costs of this study are financed by NTNU and MI Lab. Volunteers do not receive monetary compensation. At the end of the data collection part of the study volunteers will be invited to a small "thank you" reception and have a 1:30 chance of winning a gift card for 2 cinema tickets. In addition those who participate will learn about their physical condition via the VO_2 max test and may gain some insight into training and brain function.

9. Ethical approval

This study is approved by the Regional committee for medical research ethics.

10. Contact person

If you would like more information please contact:

Martin Wohlwend: wohlwend@stud.ntnu.no

Helen Palmer
MR-centre (3. etasje)
St. Olavs Hospital
7006 Trondheim
helen.palmer@ntnu.no

11. Consent

Name:_____

Date of birth:_____

I confirm that (cross in box)

       I have no medical history of heart conditions or brain disorders.

       I have read and understood the above information regarding the study.

       I am willing to participate in the study.

Date:_____

Signature:_____

Appendix C – Ethical Committee Approval

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:		Vår dato:	Vår referanse:
REK midt	Siv Tone Natland	73598916		12.09.2011	2011/1433/REK midt
				Deres dato:	**Deres referanse:**
				15.06.2011	

Vår referanse må oppgis ved alle henvendelser

Helen Palmer
MR-senteret

2011/1433 Treningsintensitet, humør og frontallappen funksjon

Forskningsansvarlig: NTNU, Det Medisinske Fakultet, Institutt for sirkulasjon og bildediagnostikk v/instituttleder Øyvind Ellingsen
Prosjektleder: Helen Palmer

Prosjektomtale (revidert av REK):
Hensikten med denne studien er å studere en særskilt mekanisme for treningsinduserte endringer i humør, den såkalte "exercise-induced transient hypofrontality" (eTHT). Treningen vil foregå på tredemølle og testingen omfatter Connors continuous performance test, PANAS-skjema og VO2 max. En ønsker å rekruttere 30 friske menn og kvinner i alderen 18 – 35 år gjennom oppslag på steder for studenter. Samtykke innhentes.

Forskningsetisk vurdering

Med hjemmel i lov om behandling av etikk og redelighet i forskning § 4 og helseforskningsloven (hfl.) § 10 har Regional komité for medisinsk og helsefaglig forskningsetikk Midt-Norge vurdert prosjektet i sitt møte 26. august 2011. Komiteen viser til prosjektprotokoll, målsetting og plan for gjennomføring, og finner at prosjektet har et forsvarlig opplegg som kan gjennomføres under henvisning til evt. merknader og vilkår for godkjenning, jf. hfl. § 5.

Merknader og vilkår:

- Komiteen vil presisere at prosjektmedarbeiderne har taushetsplikt i henhold til hfl. § 7. Personopplysninger skal behandles konfidensielt, og undersøkelsesresultater inkludert evt. navnelister, oppbevares forskriftsmessig.
- -Komiteen ber om at grunnlagsdata ikke blir anonymisert, slettet eller destruert, men blir oppbevart på en betryggende måte i minimum 5 år etter prosjektslutt av kontrollhensyn. Det må opplyses i informasjonsskrivet at slik oppbevaring blir gjennomført.
- -Prosjektleder skal sende sluttmelding til den regionale komiteen for medisinsk og helsefaglig forskningsetikk når forskningsprosjektet avsluttes. I sluttmeldingen skal resultatene presenteres på en objektiv og etterrettelig måte, som sikrer at både positive og negative funn fremgår, jf. hfl. § 12.
- -Komiteen minner om at de aller fleste kliniske studier skal registreres i det offentlig tilgjengelige registeret www.clinicaltrials.gov. Prosjektleder er ansvarlig for å avgjøre om forskningsstudien omfattes av kravet til registrering.

Vedtak

"Regional komité for medisinsk og helsefaglig forskningsetikk, Midt-Norge godkjenner at prosjektet gjennomføres med de vilkår som er gitt."

Godkjenningen av prosjektet gjelder til 30.12.2011. Av dokumentasjonshensyn skal opplysningene likevel bevares inntil 30.12.2016. Opplysningene skal deretter slettes eller anonymiseres, senest innen 30.06.2017.

Opplysningene skal lagres avidentifisert, det vil si adskilt i en nøkkel- og en opplysningsfil.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren».

Prosjektet skal sende sluttmelding til REK midt på fastsatt skjema senest 30.06.2012.

I tillegg til vilkår som fremgår av dette vedtaket, er tillatelsen gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden og protokollen, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Dersom det skal gjøres endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektleder sende endringsmelding til REK. Vi gjør oppmerksom på at hvis endringene er "vesentlige", må prosjektleder sende ny søknad, eller REK kan pålegge at det sendes ny søknad.

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jfr. helseforskningsloven § 10, 3 ledd og forvaltningsloven § 28. En eventuell klage sendes til REK midt. Klagefristen er tre uker fra mottak av dette brevet, jfr. forvaltningsloven § 29.

Vi ber om at alle henvendelser sendes inn via vår saksportal: http://helseforskning.etikkom.no eller på e-post til: post@helseforskning.etikkom.no.

Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen,

Sven Erik Gisvold
Professor dr.med
Leder REK Midt

Siv Tone Natland
Rådgiver
REK Midt

Kopi til: oyvind.ellingsen@ntnu.no, rek-isb@medisin.ntnu.no

Appendix D – PANAS Mood Score

The PANAS

This scale consists of a number of words that describe different feelings and emotions. Read each item and then mark the appropriate answer in the space next to the word. Indicate to what extent you feel this way right now, that is, in the present moment. Use the following scale to record your answers.

1 very slightly or not at all

2 a little

3 moderately

4 quite a bit

5 extremely

A   B

____interested   ____irritable

____distressed   ____alert

____excited   ____ashamed

____upset   ____inspired

____strong   ____nervous

____guilty   ____determined

____scared   ____attentive

____hostile   ____jittery

____enthusiastic   ____active

____proud   ____afraid

Appendix E – Abstract for Biomedical Basis of Elite Performance (BBEP) 2012

The effect of exercise on executive function – investigating an alternative explanation for "runner's high"

M Wohlwend[1], A Olsen[1], AK Håberg[2], HS Palmer[1].

1. Department of Circulation and Medical Imaging, 2. Department of Neuromedicine, Norwegian University of Science and Technology, Trondheim, Norway.

The exercise induced transient hypofrontality theory (eTHT) has been proposed as an alternative neurophysiological explanation for the mood and cognition enhancing effect of aerobic exercise (Dietrich, 2003), popularly known as "the runner's high". In light of the computational demands of movement, eTHT hypothesises that hypoactivity occurs, particularly in the prefrontal cortex during exercise. The prefrontal cortex is involved in executive function (Aron, 2004). The current study used the Connor's Continuous Performance Test (CCPT) to investigate changes in attention and executive control during and post treadmill running exercise in young healthy volunteers (n=30, 15 male, 15 female). Subjects performed a VO_2max test to assess aerobic capacity and maximum heart rate (MHR). In separate sessions, for which the order was randomised subjects performed CCPTs at rest and during low intensity (LI; 63 % MHR) and moderate intensity (MI; 75 % MHR) treadmill running exercise. In a second phase of the study subjects performed isocalorifically matched exercise bouts, in separate sessions in a randomised order, of LI, MI and high intensity interval training (HIT). The HIT session consisted of 4x4 intervals: 4x4 min 90 % MHR with 3 min recovery at 60-70 % MHR. For the statistical analysis repeated measure ANOVAs were done for both the during exercise and the post exercise tests.

Preliminary statistical analyses of the CCPT results gave the following results. Values are means ± S.E.M., compared by ANOVA. Choice reaction time (HitRT) increased significantly during exercise (LI 323.2 ± 34.1 ms; MI 324.1 ± 34.4 ms) compared to at rest (309.1 ± 39.4 ms; $p \leq 0.005$). Commission errors, an indicator of executive control or impulsivity were not significantly different during exercise, compared to at rest but showed a trend to increase during exercise compared to baseline (p=0.08).

The findings for the post exercise CCPTs showed that choice reaction time (HitRT) decreased significantly from rest (309.1 ± 39.4 ms) to post exercise levels (LI 282 ± 36 ms; MI 276.6 ± 33.95 ms; HI 275 ± 30.9 ms) in an exercise intensity dependent, linear fashion ($p \leq 0.0001$). Commission errors were not significantly different post exercise, compared to at rest but showed a linear increasing trend with intensity (p=0.075).

The main preliminary findings of the current study are that volunteers made the same level of commission errors during exercise and at rest, regardless of exercise intensity. The lack of change in impulsive errors during exercise paired with increasing reaction times during running may imply reduced activity in the prefrontal cortex during exercise, consistent with eTHT. According to the post exercise CCPT results hitRT was decreased post exercise compared to rest, with a linear trend for exercise intensity ($p \leq 0.0001$). This may imply prefrontal cortex hyperactivity post exercise and thus has implications for elite performance in a variety of sports.

Appendix F – Poster BBEP 2012

## The effect of exercise on executive function - investigating an alternative explanation for "runner's high"

M. Wohlwend[1], A. Olsen[1], A. K. Håberg[2], H.S. Palmer[1].

[1] MI-Lab, Dept. of Circulation and Medical Imaging; [2] Dept. of Neuroscience, NTNU, Trondheim, Norway

NTNU
Norwegian University of Science and Technology

BACKGROUND

Due to the computational and metabolic demands during exercise the brain is hypothesised to shift its limited ressources from areas that can afford to disengage (Hypofrontality Theory: Dietrich, 2003) - such as **executive networks**.
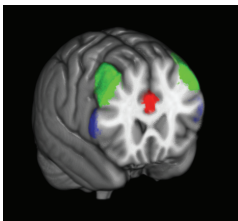
Green: Dorsolateral prefrontal cortex (DLPFC)

Blue: inferior frontal Cortex (IFC) pars opercularis

Red: Anterior Cingulate Cortex (ACC)

The primary aim of the current study was to investigate the effect of different exercise intensities on executive function during and post treadmill running.

METHODS

30 young, healthy volunteers with a normal sleeping rhythm (24.3 ± 3.3 yr, VO2max 54.9 ± 3.7 ml/kg/min; 15 male, 15 female) underwent **Conner´s Continuous Performance Test (CCPT).** They were presented with visual stimuli (letters from A to Z) at different Interstimulus Intervals (1,2 and 4sec). **Reaction time and Commission errors** were acquired.

The CCPT test: consists of 6 randomised blocks with the 3 different ISIs (1,2 and 4sec)
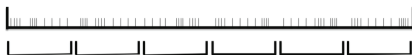
VO2max and maximum heart rate (MHR) of the volunteers were measured during treadmill running. In an randomised order, CCPTs at rest and during low intensity (LI; 63 % MHR) and moderate intensity (MI; 75 % MHR) treadmill running were carried out.
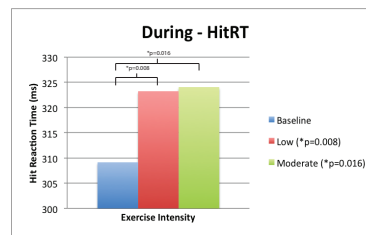
In the second phase of the study volunteers performed isocalorifically matched exercise bouts, in separate sessions in a randomised order, of LI, MI and a high intensity interval training session (HI). Statistical analysis consisted of repeated measure ANOVAs, Bonferroni-adjusted post-hoc analyses and polynomial trend analyses.
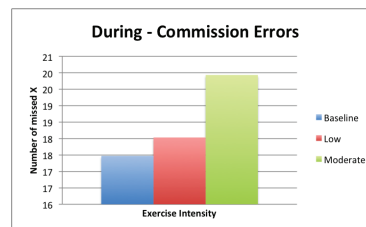
Example of CCPT screen: "click on every letter except X as fast as you can but also as accurately as possible throughout the whole test"
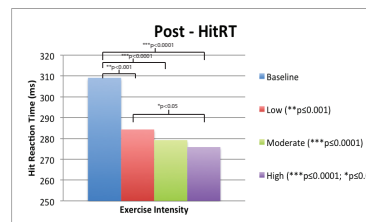
A

X

RESULTS

During - HitRT

Hit Reaction Time (ms)

Exercise Intensity

- Baseline
- Low (*p=0.008)
- Moderate (*p=0.016)

DURING exercise **HitRT**: increased significantly (LI 323.2 ± 34.1 ms; MI 324.1 ± 34.4 ms) compared to at rest (309.1 ± 39.4 ms; $F(2, 58) = 7.48$, $p \leq 0.001$) with a significant linear trend ($p \leq 0.005$).

During - Commission Errors

Number of missed X

Exercise Intensity

- Baseline
- Low
- Moderate

DURING exercise **Commission errors**: not significantly different compared to at rest ($F(2, 58) = 3.58$, $p=0.057$) but showed a linear trend to increase in a exercise dependent fashion ($p \leq 0.05$).

Post - HitRT

Hit Reaction Time (ms)

Exercise Intensity

- Baseline
- Low (**p≤0.001)
- Moderate (***p≤0.0001)
- High (***p≤0.0001; *p≤0.05)

POST exercise **HitRT**: decreased significantly from rest (311.2 ± 38.5 ms) to post exercise levels (LI 284.3 ± 34.5 ms; MI 279.7 ± 31.9 ms; HI 275.2 ± 29.4 ms; $F(1.79, 46.51) = 24.06$, $p \leq 0.0001$, $\omega = 0.36$) in an exercise intensity dependent, linear fashion ($p \leq 0.0001$).

Post - Commission Errors

Number of missed X

Exercise Intensity

- Baseline
- Low
- Moderate
- High
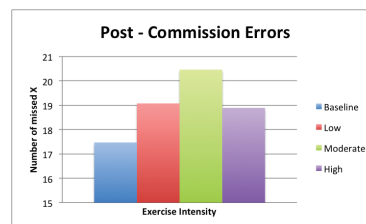
POST exercise **Commission errors**: not significantly different ($F(3, 78) = 2.68$, $p > 0.05$), compared to at rest but showed a significant quadratic trend ($p < 0.05$).

CONCLUSION

An increase in processing time (intensity independent) and a non-significant trend for an intensity-dependent increase in impulsivity errors **during** running may imply a state of hypofrontality.

A significant decrease in processing time paired with no significant difference in impulsivity errors suggests hyperfrontality **post** running exercise.

These findings suggest that the computational demand of running impairs executive function. In particular, executive control, whose circuits are found in the prefrontal cortex, appears to be affected by running, immediately at the onset of exercise.

Dietrich A (2003) Functional neuroanatomy of altered states of consciousness: the transient hypofrontality hypothesis. Conscious Cogn 12:231-256.

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Appendix G – Abstract for Society for Neuroscience (SfN 2012)

Investigating the reticular-activating hypofrontality model of acute exercise with Conner´s Continuous Performance test in combination with treadmill running and transcranial direct current stimulation.

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Abstract:
The reticular-activating hypofrontality model of acute exercise (RAH) was proposed to explain the mood and cognition enhancing effect of aerobic exercise[1]. RAH predicts exercise-induced hypoactivity in frontal cortex, which mediates executive function[2]. Connor's Continuous Performance Test (CCPT) was used to investigate changes in executive function during and 5min post treadmill running exercise in young healthy volunteers (n=30, 15 male). In separate sessions, in a randomized order, subjects performed the CCPT at rest, during low- (LI; 63% maximum heart rate; MHR) and moderate intensity (MI; 75% MHR). In the second part of the study subjects performed isocalorifically matched exercise bouts of LI, MI and high intensity interval training (HIT) consisting of 4x4 intervals: 4x4 min 90% MHR with 3 min recovery at 60-70% MHR. Repeated measures ANOVAs revealed main effects of exercise intensity for Hit reaction time (HitRT) during exercise ($F(2, 58) = 7.48$, $p \leq 0.001$), and HitRT post exercise ($F(1.79, 46.51) = 24.06$, $p \leq 0.0001$). Subsequent analyses showed an overall increase of HitRT during exercise compared to rest ($p \leq 0.005$). HitRT decreased significantly from rest to post exercise levels in an exercise intensity dependent, linear fashion ($p \leq 0.0001$). Commission errors showed a non significant linear trend to increase both during ($p=0.057$), and post exercise ($p=0.052$) as a function of intensity. These results could be taken to support the view that during exercise hypofrontality is the brain's response to the high computational demand of running. The differences observed during and post exercise suggest that different computational and metabolic factors may be differentially active in determining frontal activity at different time points in exercise and recovery.

A separate study tested the relationship between the exercise effects and levels of frontal cortex activity. Frontal cortical excitability was modulated by cathodal transcranial direct current stimulation (tDCS) over the left dorsolateral prefrontal cortex. This tDCS induced reduction in frontal activity whilst at rest

was able to reproduce the effects observed post exercise, ie faster HitRT, more commission errors. Anodal tDCS increased frontal lobe activity in the immediate post exercise period but was unable to modify the post exercise effects, supporting the view that different factors operate to elicit during and post exercise effects.

Taken together, these results, and other CCPT results (not shown), may be interpreted as reduced frontal activity during and post exercise.

1 Dietrich A et al. (2011). Neurosci Biobehav Rev 35, 1305-1325.
2 Aron AR (2004). TRENDS in Cogn Sci 8, 170-177.