The assessment of acute, exercise-induced changes in resting state brain networks applying EEG-based graph theory

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DANIEL BÜCHEL

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Principle supervisor

Prof. Dr. rer. medic. Jochen Baumeister

Exercise Science & Neuroscience Unit

Paderborn University

Germany

Secondary supervisor

Prof. Dr. rer. nat. Øyvind Sandbakk

Department of Neuromedicine and Movement Science

Norwegian University of Science and Technology

Norway

Paderborn, January 20, 2023

Declaration of Authorship

I declare to have read and accepted the Ph.D. regulations of the Faculty of Sciences, University of Paderborn (no. 10.21 / 12, 31-03-2021). Furthermore, I declare that the work presented in the present thesis is original and the result of my own work, except as acknowledged, and has not been submitted, neither in parts nor as a whole, for any other degree or qualification at any University. Content and ideas taken from other sources are - to the best of my knowledge and belief - cited correspondingly. As such, I declare that the research presented in the included studies was conducted in absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Daniel Büchel, Paderborn, January 20 2023

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Abstract

Acute exercise has been shown to transiently modulate brain function of the individual in a dose-specific manner, with either positive or negative effects on neural processes and sports performance. However, an integration of the brain into exercise physiology is lacking since available neuroimaging techniques are immobile or movement susceptible. Therefore, the present study aimed to explore the interaction between exercise and brain function through the portable assessment of electroencephalography (EEG) resting state networks (RSNs). In Study I, participants were exposed to an incremental treadmill protocol with intermittent EEG recordings. The study revealed that the RSN approach allows for the quantification of intensity-specific modulations of brain function. After observing exercise-induced modulations of RSNs in the initial study, Study II quantified the reliability of the examined RSN outcomes. Data indicated a range of poor to excellent reliability scores for RSN outcomes, with particularly good reliability scores after exercise. Study III aimed to explore the effect of exercise mode on RSNs. Therefore, cross-country skiers performed two incremental treadmill protocols, one in a running mode and one in a skiing mode. The performed exercise mode was found to further influence the transient modulation of RSNs. Overall, this thesis points out that exercise and brain function interact in a dose-specific manner, in which the energetic (intensity) and sensorimotor demands (mode) of exercise seem to affect brain function differentially. The RSN approach seems feasible to explore the dose-response-relationship between exercise and brain function to better understand the brain's role in exercise physiology.

Zusammenfassung

Sportliche Belastung beeinflusst die Gehirnfunktion kurzzeitig und Dosis-spezifisch, sodass neuronale Prozesse und sportliche Leistung entweder positiv oder negativ beeinflusst werden. Dennoch wird das Gehirn in der Leistungsphysiologie nur wenig berücksichtigt, da neurophysiologische Methoden immobil oder bewegungsanfällig sind. Die vorliegende Arbeit untersuchte daher die Interaktion zwischen Belastung und Gehirn durch die portable Messung elektroenzephalographischer (EEG) Ruhenetzwerke (RSNs). In Studie I absolvierten die Probanden ein Stufenprotokoll auf dem Laufband mit intermittierenden EEG Messungen. Die Studie zeigte, dass der RSN Ansatz die Messung intensitätsspezifischer Veränderungen der Gehirnfunktion ermöglicht. Nach den initialen Beobachtungen in der ersten Studie zielte Studie II darauf ab, die Reliabilität der RSN Parameter zu messen. Die Auswertung ergab schlechte bis exzellente Reliabilitäten der RSN Parameter, wobei speziell nach Belastung gute Reliabilitäten vorlagen. Studie III untersuchte den Effekt verschiedener Belastungsmodi auf die RSNs. Dafür absolvierten Skilangläufer zwei Belastungsprotokolle auf dem Laufband, je einmal laufend und skilaufend. Der Modus beeinflusste dabei die Veränderungen des RSNs zusätzlich. Insgesamt zeigt diese Dissertation somit, dass Belastung und Gehirnfunkton portabel gemessen werden können und dosis-spezifisch interagieren. Hierbei induzieren die energetischen und sensomotorischen Aspekte der Belastung differentielle Effekte. Der RSN Ansatz ermöglicht demnach die Untersuchung der Dosis-Wirkungs-Beziehung von Belastung und Gehirnfunktion und könnte das Wissen über die Rolle des Gehirns in der Leistungsphysiologie verbessern.

Table of contents

List of Publications

Study I (Büchel, Sandbakk, et al., 2021)

Exploring intensity-dependent modulations in EEG resting-state network efficiency induced by exercise (2021)

Büchel D, Sandbakk Ø & Baumeister J

European Journal of Applied Physiology, 121(9):2423-2435

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Study II (Büchel, Lehmann, Sandbakk, et al., 2021)

EEG-derived brain graphs are reliable measures for exploring exercise-induced changes in brain networks (2021)

Büchel D, Lehmann T, Sandbakk Ø & Baumeister J

Scientific Reports, 11: Article number 20803

DOI: 10.1038/s41598-021-00371-x

Study III (Büchel et al., 2023)

The mode of endurance exercise influences changes in EEG resting state graphs among high-level cross-country skiers (2023)

Büchel D, Lehmann T, Torvik PØ, Sandbakk Ø & Baumeister J

Medicine & Science in Sports & Exercise, Accepted ahead of publication

DOI: 10.1249/MSS.0000000000003122

List of figures

List of tables

List of abbreviations

AMICA	-	Adaptive Mixture Independent Component Analysis
ASR	-	Artifact subspace reconstruction
B_{La}	-	Blood lactate concentration
BOLD	-	Blood-oxygenation-level-dependent contrast
BS	-	Borg Scale
BDNF	-	Brain-derived neurotrophic factor
CNS	-	Central Nervous System
CBF	-	Cerebral blood flow
PL	-	Characteristic Path Length
CC	-	Clustering Coefficient
CoV	-	Coefficient of Variation
XC	-	Cross-Country
ECG	-	Electrocardiogram
EEG	-	Electroencephalography
FC	-	Functional Connectivity
fMRI	-	Functional magnetic resonance imaging
fNIRS	-	Functional Near-Infrared Spectroscopy
HR	-	Heart Rate
IC	-	Independent Component
ICA	-	Independent Component Analysis
IGF-1	-	Insulin-like growth factor-1
ICC	-	Intraclass-Correlation-Coefficient
VO^2_{peak}	-	Peak oxygen uptake

RPE	-	Rating of perceived exertion
RSN	-	Resting State Networks
SWI	-	Small-World-Index
vVO^2_{peak}	-	Speed at maximal oxygen uptake
wPLI	-	Weighted Phase-Lag-Index

1 Background

Sports training consists of systematically prescribed doses of exercise meant to improve, recover or maintain body function and sports performance (Viru & Viru, 2000). In order to prescribe adequate training stimuli serving for the improvement of body function, the physiological responses of the individual to a given dose of exercise must be controlled and anticipated (Viru & Viru, 2000). The process of controlling and adapting training stimuli is referred to as training monitoring and is an essential part of the systematic training process. Training monitoring builds up on the recording of physical, physiological, and subjective information on the individual before, during, and after exposure to exercise (Halson, 2014). Since the human body is an adaptive organism, the monitoring of physiological responses to prescribed doses of exercise over time is essential to identify the physiological training status of the individual with regard to performance adaptation, stagnation, and maladaptation (Bourdon et al., 2017).

The data utilized for training monitoring can be categorized into external and internal load variables. External load measures quantify the physical training stimuli an individual is exposed to. On the one hand, quantitative aspects such as duration, distance, velocity, or resistance specify an individual´s work independent from individual physiological characteristics. On the other hand, qualitative aspects of a prescribed bout of exercise such as the conducted exercise mode allow for a further specification of the individual´s work (Ø. Sandbakk et al., 2021). Together, the entity of all quantitative and qualitative characteristics resemble the dose of an acute bout of exercise (Wasfy & Baggish, 2016). In addition to the work an athlete is exposed to, the measures of internal load refer to the acute responses of the physiological system reacting to a prescribed dose of exercise. Frequently monitored physiological variables are the heart rate (HR) and blood lactate concentrations (B_{La}) to objectively quantify cardiovascular or metabolic responses to exercise objectively. Further, subjective outcomes such as the rate of perceived exertion (RPE) quantify the psychophysiological response of the individual to exercise (Haddad et al., 2017). The measures of external and internal load are highly interconnected since the response of the physiological systems – the internal load – depends on the characteristics of the given training dose – specified by the external load. Accordingly, the exercise dose determines the magnitude of the acute response of the involved physiological systems (Selye, 1956). Consistent exposure to prescribed doses of exercise is suggested to initiate chronic functional and structural adaptations of the involved physiological systems, also referred to as the training effect (Viru & Viru, 2000). These adaptations aim to increase the capacity of the physiological system, improve its resistance toward subsequent doses of exercise, and therefore improve sports performance.

Apart from the important role of the cardiovascular and metabolic systems to provide and distribute the energy required for exercise, the generation of movement also requires functional contributions from the central nervous system (CNS). The CNS is the physiological system responsible for the processing and integration of environmental and movement-related information and is therefore decisive for performance-relevant processes contributing to cognition (Shenhav et al., 2017) and sensorimotor control (Baumeister, 2013). Thus, the billions of neurons in the CNS interact to i) perceive sensory information from the body and the external environment, ii) process exercise-related sensory information, and iii) integrate this information to generate an adequate motor output (Baumeister, 2013). Depending on the concrete affordance of the performed bout of exercise, different neural ensembles are involved in the perception and processing of task-relevant information to generate the required movements (Yarrow et al., 2009). So, the activation and communication of neural resources to process information for sensorimotor control and cognition is essential for the generation of movement and makes the brain an important component in exercise physiology (Yarrow et al., 2009).

Apart from the complex demands on the CNS during exercise which arise from the processes of sensorimotor control, the acute responses of the metabolic and cardiovascular system originating in the brain periphery reach out to the CNS. For instance, exercise-released substrates such as lactate cross the blood-brain-barrier and modulate the activity of nerve cells (Pedersen, 2019; Vints et al., 2022). Depending on the characteristics of the prescribed dose of exercise, these processes can either facilitate or dampen the central nervous processes underlying sensorimotor control and cognition (Lambourne & Tomporowski, 2010; McMorris et al., 2015). For this reason, dose-dependent up- and downregulations after acute bouts of exercise have been reported for the cortical processing of task-relevant information (Gusatovic et al., 2022), but also for the efferent recruitment of motor units to generate movement (Turco & Nelson, 2021). In consequence, the dose-response-relationship between the CNS and prescribed doses of exercise can be stated as complex and non-linear. In this complex relationship, the impact of the qualitative characteristics of the exercise dose, e.g. the exercise mode and the demands on sensorimotor control, are almost unconsidered yet (Pesce, 2012). Especially for sports with energetic and sensorimotor demands, these aspects of the exercise dose may affect neural processes additionally (Habay et al., 2021). However, the contributions of the CNS to the processes of sensorimotor control and the effect of peripheral phenomena on neural processing assume that the brain plays a complex and important role in exercise physiology and sports performance. Consequently, integration of the brain into our understanding of exercise physiology seems imperative to understand the interplay between exercise and human performance.

Nevertheless, the integration of CNS measures are highly underrepresented in exercise physiology research (Perrey, 2022; Seidel-Marzi & Ragert, 2020). This is due to two major issues: neurophysiological methods require a high technical effort and are highly affected by movement artifacts (Perrey & Besson, 2018). Therefore, coaches and scientists prefer to monitor behavioral changes associated with the perception, processing, and integration of sensory information as indirect underpinnings of altered CNS function (Perrey, 2022). For instance, cognitive tests assessing reaction times and task accuracies provide insights into the individual's ability to perceive and process task-relevant information (Skala & Zemková, 2022). Further, neuromuscular tests such as the counter movement jump (Balsalobre-Fernańdez et al., 2014) or sports-specific drills (McMorris & Hale, 2012) measure the ability to integrate sensory information into motor control. However, the interpretation of behavioral measures as underpinnings of brain function remains domain-specific and is highly influenced by individual factors such as skill level and task demands (McMorris et al., 2015). Ergo, integrating measures into exercise physiology research that are directly derived from the brain may allow for the quantification of altered CNS function in a more holistic and less-biased manner.

Non-invasive technologies like functional magnetic resonance imaging (fMRI) (Herold et al., 2020), electroencephalography (EEG) (Gramkow et al., 2020; Hosang et al., 2022) or functional near-infrared spectroscopy (fNIRS) (Salzman et al., 2022) allow measuring alterations in CNS function associated with prescribed doses of exercise directly. These neurophysiological changes can be quantified based on changes of activity in different brain regions, but also through changes in the communication across these brain regions. For instance, recent developments in EEG technology allow for a faster and more portable assessment of neurophysiological data in the context of exercise neuroscience research (di Fronso et al., 2019; Park et al., 2015). These developments may be beneficial to reduce the technical effort of neurophysiological applications and integrate the brain into exercise physiology research.

Therefore, the present thesis aimed to explore the dose-response-relationship between acute exercise and CNS function through a portable neurophysiological approach based on the EEG. The portable assessment of brain function to quantify exercise-brain interactions could help to overcome issues of applicability, which are the key obstacles to the integration of the CNS in exercise physiology research.

1.1 How acute exercise modulates neural activity

During exercise, the brain is continuously receiving information from visual, vestibular, auditory, and somatosensory receptors which allow for the adaptation of behavior in dynamic environments. This information enters the CNS through action potentials generated by specialized receptors and propagates to the structures of the CNS via axons. Hereof, precise processing of the electrical information due to the neurons in the CNS is mandatory for an adequate generation of motor behavior concerning the time, space, and magnitude of movement (Baumeister, 2013). Taking this into account, the precise interplay between the neurons involved in sensorimotor control and cognition seems to be imperative for sports performance.

During and after exercise, this interplay can be transiently modulated due to physiological processes initiated in the body periphery which reach out to the cells of the CNS (El-Sayes et al., 2019). More precisely, every single bout of exercise initiates a cascade of short-term physiological responses that start on the molecular level and finally modulate the functional activity and connectivity of neural ensembles (El-Sayes et al., 2019). This cascade of processes acutely affecting brain function starts with the release of so-called exerkines in the brain's periphery. Exerkines are defined as a group of substrates including peptides, metabolites, and nucleic acids that are released to the blood from physiological systems like the muscles or the liver under exercise conditions (Chow et al., 2022; Vints et al., 2022). During and also after acute bouts of exercise, these substrates show an

increased level of serum concentration (Vints et al., 2022). Via the exercise-induced activation of metabolism and upregulation of cerebral blood flow (CBF), exerkines pass the blood-brain-barrier and interact with the cells of the CNS (J. C. Smith et al., 2010).
Once arrived at the nerve cell, exerkines actively modulate cellular activity by affecting the processes at the presynaptic and postsynaptic membrane and subsequently modulate the excitability of the single neuron (Vints et al., 2022). While the accumulation of exerkines such as brain-derived neurotrophic factor (BDNF), Insulin-like growth factor-1 (IGF-1), and lactate is primarily associated with beneficial effects on synaptic transmission (Vints et al., 2022), lactate also serves as an energy source for the underlying neural processes (Magistretti & Allaman, 2018; Proia et al., 2016). Furthermore, exerkines such as myokines and adiponectin promote brain function indirectly due to an upregulation of BDNF production once they pass the blood-brain-barrier (Chow et al., 2022). Since an elaboration of the specific pathways and effects of the exerkines would exceed the scope of the present thesis, the reader is referred to the review of Vints and colleagues (2022) for further information. Nevertheless, it is worth noting that the acute release of exerkines also seems to play a key role in chronic adaptations of the brain to exercise through their involvement in the long-term potentiation of synapses (Draganski & May, 2008). Long-term potentiation is defined as the chronic, activity-dependent strengthening of neural connections based on recent activity patterns and is one of the main processes contributing to functional adaptations of the brain (Steele & Mauk, 1999). Since exerkines acutely modulate synaptic transmission, they are also related to long-term potentiation under circumstances of chronic exercise (Vints et al., 2022).
When exerkines pass the blood-brain-barrier, they propagate to the cells of the CNS and modulate the activity at the pre- and postsynaptic neuron through specific interactions with membrane receptors (Vints et al., 2022). Consequently, the electrical activity of receptors in the neuronal membrane changes and alters neuronal excitability and synaptic transmission, e.g. in neurons of the motor cortex (Singh & Staines, 2015). Next to the neuron, neuroglia such as astrocytes also contain receptors responsive to exerkines (F. Li et al., 2021). Through the interaction with glial cells, exerkines such as BDNF further modulate postsynaptic transmission by influencing conduction velocity and signal propagation (F. Li et al., 2021). Therefore, not only the synaptic transmission at the nerve cell changes in response to exercise but also the electrophysiological milieu surrounding

the nerve cell. Since smaller neural patches in the brain are highly interconnected with close- and far-distant ensembles, the modulation of local excitability and neuroglia environment is likely to result in modulations of the functional properties of bigger neural pathways and functional units (Harris et al., 2019). So, the release of exerkines is likely to result in transient and large-scale modulations of brain function.

Besides the release of exerkines, another factor contributing to altered neurophysiological activation is the change in CBF. Through an increased need for oxygen supply in the whole body, CBF increases when the individual is involved in exercise (K. J. Smith & Ainslie, 2017). The increase in CBF is also stated as intensity-dependent and biphasic, since i) CBF increases until exercise intensity of about 60 % of individual aerobic capacity and ii) plateaus at intensities > 60 % (J. C. Smith et al., 2010; K. J. Smith & Ainslie, 2017). The increase in CBF comes along with an improved oxygen delivery as well as an upregulation of cerebral proliferation related to glucose, lactate, but also the above-introduced exerkines. Thus, changes in CBF further support brain function during and after exercise by increasing the activity of the nerve cells.

Taken together, exercise-related changes in metabolism and the activation of physiological systems induce cross-talks between different physiological systems and the CNS during and after acute bouts of exercise. The release of exerkines and the upregulated proliferation of the brain cells modulate synaptic activity and excitability and pave the way for large-scale functional changes in brain function (El-Sayes et al., 2019). Based on the model of external and internal load, a dose-response-relationship between the prescribed dose of exercise and the acute response of the CNS might be hypothesized. In the upcoming chapter, the effect of exercise characteristics on the induced modulations of brain function will be summarized.

1.2 Dose-response relationships between exercise and the brain

The prescription of a training dose determines the subsequent physiological responses of the involved physiological systems. The most important variables to define and anticipate physiological responses follow the so-called “FITT principle” (Ferguson, 2014; Herold et al., 2019). The “FITT principle” specifies a training dose based on the quantitative exercise characteristics of frequency, intensity, and time and the more qualitative aspect of type/mode. Since exercise frequency refers to the number of times a specific exercise is performed in a given time unit it displays a chronic rather than an acute dosing variable of exercise and will not be considered in the following chapter. A scoping overview of the influence of exercise intensity, time/ duration, and type/ mode as possible moderators of the interplay between acute exercise and brain function aims to emphasize the complex role of the brain in exercise physiology.

As the most investigated exercise variable, the intensity of exercise is accepted as a key moderator of the brain´s acute response to exercise (Herold et al., 2019). It is suggested that higher exercise intensities augment the release of exerkines in the body periphery and the general systemic influence on the brain due to increased metabolism. Through the increased release of exerkines in the body periphery, more substrates can pass the blood-brain-barrier and therefore augment the cross-talk between the brain and the body periphery (Chow et al., 2022). For instance, exercise intensity is stated as an important moderator of the release of BDNF, and suggested as one of the most important factors for transient and chronic changes in brain function (Dinoff et al., 2017). Further, the intensity of a bout of exercise is linearly associated with the B_{La} concentration. Since lactate serves as both a signaling molecule but also an energy source for cerebral metabolism, peripheral metabolic demands seem to also affect neural processes by facilitating neural activity (Hashimoto et al., 2018; Magistretti & Allaman, 2018). Moreover, increasing exercise intensities to ≤ 60 % of individual aerobic capacity increases total CBF and facilitates neural activity increasing the energetic supply of the brain cells (J. C. Smith et al., 2010). Accordingly, the intensity of a bout of exercise influences neural processing due to higher activation of the physiological systems contributing to the exerkine release and the increased distribution of these substrates based on altered metabolic demands of the nerve cells.

Intensity-specific modulations in brain function can also be quantified due to the application of non-invasive neurophysiological techniques. For instance, Schmitt et al (2019) reported intensity-specific modulations of resting-state brain networks derived from fMRI after exercise. While both moderate and high-intensity exercise induced increased connectivity in attention-related brain networks, high-intensity exercise was specifically associated with reductions of connectivity in sensorimotor brain networks (Schmitt et al., 2019). Further, the suggestion of intensity-specific modulations of large-scale brain function is supported by EEG data published by Tamburro et al. (2020).

During an incremental cycling protocol, the authors reported improved communication efficiency in sensorimotor brain networks during moderate exercise intensities, while these facilitations disappeared at higher exercise intensities (Tamburro et al., 2020). Also, fNIRS findings from Rupp & Perrey (2008) recorded throughout an incremental cycling protocol support this dose-response-relationship. The authors reported increases in cortical oxygenation in relationship to increased exercise intensity at the initial stages of protocol, while a reduction in oxygenation was observed when the participants approached exhaustion (Rupp & Perrey, 2008). Taken together, all examples demonstrate that moderate to high-intensity exercise upregulates brain function, while this effect recedes when approaching maximal exercise intensities. Therefore, the dose-response relationship between exercise and brain function seems to follow a non-linear fashion, since beneficial effects most likely appear at moderate to high exercise intensities, but not at low or maximal exercise intensities (McMorris & Hale, 2012).

The non-linear dose-response-relationship likely results from a time-lagged process initiated by severe, exhaustive exercise intensities, which leads to a substantial release of stress hormones and catecholamines in the body periphery (Zouhal et al., 2008). Stress hormones and catecholamines such as noradrenaline and dopamine cross the blood-brain-barrier and modulate signal transmission in functional brain regions relevant to attentional processes such as the prefrontal cortex (Arnsten, 2009). In the case of spillover in given brain regions due to heavy accumulation, catecholamines bind to lower affinity receptors which have a dampening effect on neural activation (Arnsten, 2009). Due to the important contributions of the prefrontal cortex to perception and cognition, the functional capacity of the brain is reduced temporarily due to the dampening activation of prefrontal cortex neurons (Arnsten, 2009). Further, changes in CBF may contribute to dampened brain function at maximal exercise intensities. As reported by Bao et al. (2019), global CBF decreased in comparison to baseline following a time-to-exhaustion cycling trial approaching maximal exercise intensity (Bao et al., 2019). Besides a global decrease in CBF, particularly strong reductions in blood flow were observed in motor-related brain areas (Bao et al., 2019). Hence, exercise intensity is a key factor for modulations of brain function through exercise (Herold et al., 2019; Hortobágyi et al., 2022) and acts in a non-linear manner due to intensity-specific cross-talks between the brain and the body periphery.

An exercise variable inversely related to exercise intensity and the physiological cross-talks between the brain and the body is the duration or time of a bout of exercise. Based on behavioral observations, a minimal exercise duration of 10 minutes seems to be required to improve cognitive domains such as reaction time and response accuracy acutely (Cantelon & Giles, 2021; Y. Chang et al., 2012). The authors suggested that the initiation of processes in the brain periphery which facilitate brain function like exerkine release and the upregulation of CBF require a minimum time of activity (Y. Chang et al., 2012). A meta-analysis conducted by Dinoff et al. (2017) concludes that the release of BDNF and its facilitative effect on brain function is significantly affected by exercise duration and is particularly higher for exercise durations > 30 minutes (Dinoff et al., 2017). However, it is worth noting that exercise paradigms in the cited meta-analysis were pooled for exercise duration independent of the actual exercise intensity. Since the majority of the studies in the field focus on exercise intensity and implement standardized durations at different exercise intensities, specific information on exercise duration effects is sparse (Cantelon & Giles, 2021). Particular investigations on the duration-dependent release of BDNF reported no significant differences comparing 20 minutes of exercise to bouts of 30 or 40 minutes, respectively (Schmidt-Kassow et al., 2012; Schmolesky et al., 2013). Apart from behavioral and neurochemical observations, neurophysiological studies analyzing the effects of exercise length on brain activity are also rare. For instance, Woo et al (2009) compared the effect of intensity-matched exercise protocols lasting 15, 30, and 45 minutes on the asymmetry of frontal brain activation using EEG (Woo et al., 2009). In the study, the strongest modulation was observed after 30 minutes of exercise (Woo et al., 2009). Due to the association of frontal asymmetry with emotional processing, the authors suggested a positive relationship between exercise duration and mood-associated brain processes. Despite limited evidence of duration effects on brain function, it might be hypothesized that bouts of exercise that are too short may fail to initiate beneficial responses of the CNS.

Further, bouts of exercise that are too long (> 120 min) may induce detrimental effects on brain function due to the accumulation of metabolites and accompanying processes such as dehydration (Goodall et al., 2014; Kempton et al., 2011). In particular, dehydration is assumed to affect overall brain volume and dampen communication across the scalp by impairing the electrophysiological milieu (Kempton et al., 2011). Thus, a state of dehydration may result in an earlier reach of an individual's capacities in neural processing as compared to a well-hydrated state (Kempton et al., 2011). In summary, evidence from behavioral data and limited insights from neurophysiological investigations suggest a duration-specific interaction between exercise duration and brain function, where too short and too long durations of exercise may result in no effects or detrimental effects on brain function, respectively.

Further, the dose of an acute bout of exercise is moderated by the performed type or mode of exercise. The exercise mode differentiates exercise concerning the inherent qualities of the performed activities such as the muscles included, the goal of the movement, and the sensorimotor processing required (Pesce, 2012). Regarding the dose-response relationships between exercise and CNS function, Voelcker-Rehage & Niemann (2013) categorized exercise modes according to the underlying physiological processes into physical and sensorimotor modes of exercise. Physical exercise modes such as endurance and resistance activities majorly rely on metabolic processes taking place in the brain periphery (Voelcker-Rehage & Niemann, 2013). Such modes are suggested to modulate brain function through the initiation of peripheral processes such as the exerkine release (Netz, 2019). In contrast, motor or sensorimotor modes of exercise majorly rely on neurophysiological processes related to task-relevant information processing through the structures of the CNS (Voelcker-Rehage & Niemann, 2013). These modes are suggested to modulate brain function due to the specific pre-activation of neural ensembles involved in sensorimotor and cognitive processes (Netz, 2019). Therefore, the exercise mode specified by aspects such as muscles included or sensorimotor demands could further modulate the effects of acute exercise on brain function. So far, the evidence on the mode-specific effects of exercise on brain function is limited. For instance, Ueta et al. (2022) compared the acute effects of balance and walking exercises on sensorimotor brain networks derived from fMRI data. The authors reported mode-specific upregulations of brain areas, pointing toward a differential effect depending on the physical and motor demands of an acute bout of exercise (Ueta et al., 2022). Further, Brümmer et al (2011) compared acute changes in brain activity between upper- and lower-body endurance exercise modes and observed region-specific upregulations of cortical activity. While lower-limb modes such as running and cycling induced changes in the motor cortex, upper-limb modes like arm-crank exercise-induced upregulations of activity in frontal brain areas (Brümmer, Schneider, Abel, et al., 2011). Therefore, it might be suggested that the qualitative characteristics of a bout of exercise further modulate the acute exercise-induced changes in brain function apart from the energetic demands of exercise. However, due to the limited amount of evidence on mode-specific interactions between exercise and brain function, it seems important to further investigate the role of exercise mode in the dose-response-relationship between exercise and brain function.

Overall, the prescription of exercise doses employing intensity, duration, and mode seems to determine the acute exercise-induced changes in brain function. While exercise intensity and duration seem to modulate brain activity in a non-linear, intensity- and duration-dependent fashion, less is known about the effects of exercise mode. Figure 1 displays a schematic overview of the possible interaction between different exercise variables and brain function. Due to the limited amount of evidence, the proposed model resembles evidence-based as well as hypothetic interactions between dose characteristics and brain function.

For a better understanding of dose-specific interactions between acute exercise and the brain, further research is required focusing on the role of exercise mode as a potential moderator. Since different approaches grant insights into brain function, the upcoming chapter will elaborate on why the assessment of cortical resting state networks (RSNs) through EEG could be a promising methodological approach to explore the interplay between exercise and acute brain function systematically.

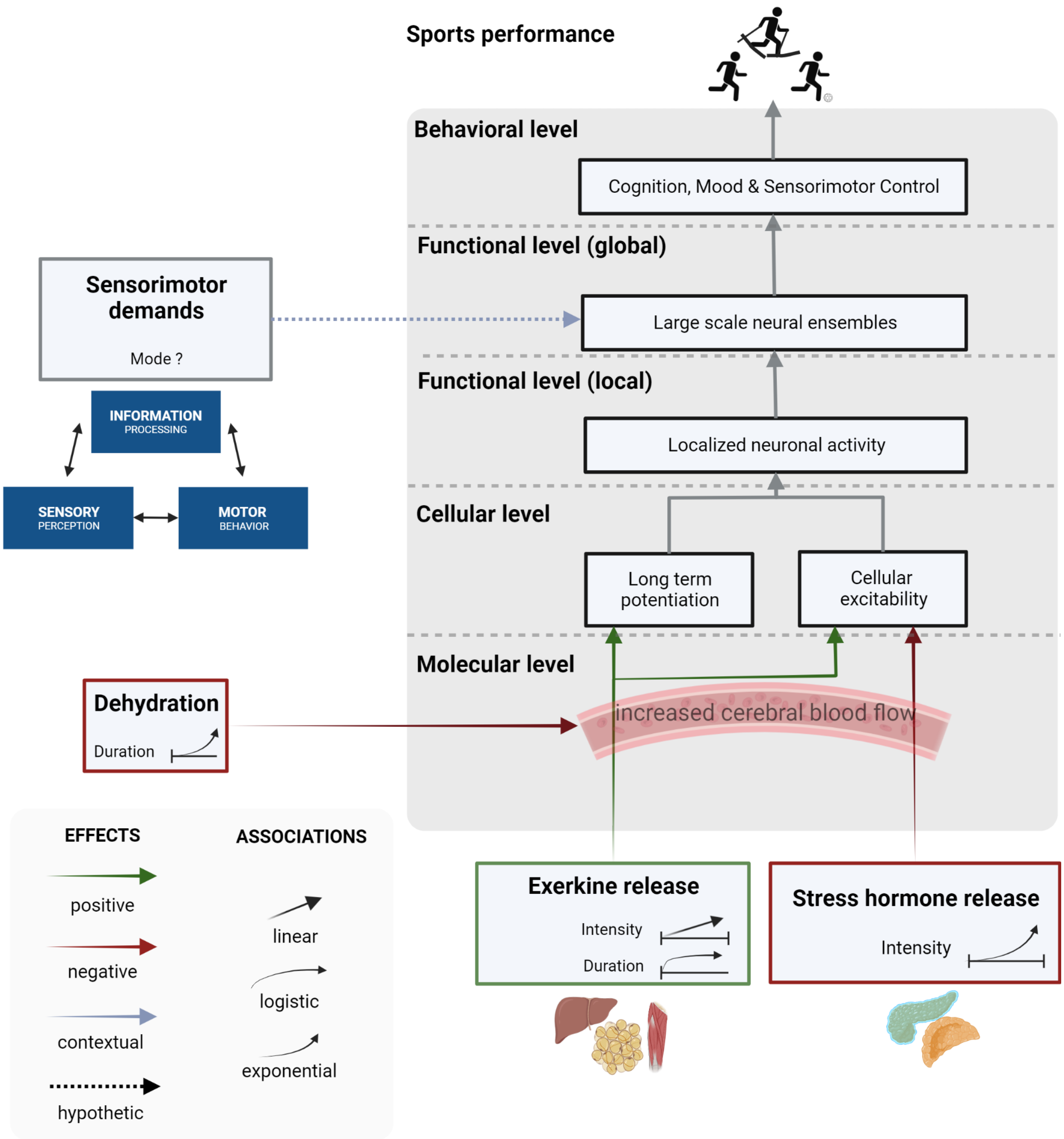

Figure 1. Overview of the exercise-induced cascade of acute changes in brain function. Processes resemble mechanisms at different scales (molecular, cellular, functional, and behavioral) which eventually result in alterations in behavior and sports performance, e.g. improved reaction time and response/movement accuracy.

1.3 The assessment of human resting state brain networks

For a long time, brain function as the entity of neurophysiological processes contributing to behavior and cognition was suggested to base on the activity of locally specialized and segregated neural patches (Stam et al., 2014). Therefore, research in exercise neuroscience research investigated the contribution of specific brain regions to sensorimotor control and sports performance extensively (S. J. Tan et al., 2019). Due to the topographical organization of the brain, various brain regions haven been identified as relevant for sports performance. For instance, the frontal cortex seems to play an important role in attentional processes (Baumeister et al., 2008), the motor cortex (Carius et al., 2021) seems to be related to task-related inhibition and motor initiation and the temporal cortices have been associated with processes of visual perception (Hülsdünker et al., 2017). Accordingly, the complex neural processes underlying sensorimotor control and cognition require the functional contribution of multiple brain areas to generate skilled and adaptive movement.

However, in the past decades, advances in neurophysiological applications contributed to convincing evidence that the brain deals with complex cognitive and behavioral affordances due to the integration of spatially segregated, but interconnected neural processes (Friston, 2002). Therefore, functional segregation and integration became two key principles of brain function (Friston, 2002). Per definition, cortical segregation describes the functional assignment of brain regions to specific aspects of cognition and/ or sensorimotor processing (Friston, 2002). Alternatively, functional integration describes the need for specialized brain regions to interact with other specialized brain regions to accommodate complex and dynamic environmental affordances (Friston, 2002). Especially for complex cognitive and sensorimotor processes, the integration of information across brain areas associated with perception, information processing, and motor execution seems imperative for adaptive behavior (Lehmann et al., 2021; Yarrow et al., 2009). Hence, modulations of functional integration due to acute exercise may affect the ability to process task-relevant information in sports substantially.

The neuronal ensembles which demonstrate an increased co-activation through functional integration, e.g. during a visuospatial reaction task, are referred to as task-positive networks (Guo et al., 2017). Further, specific brain regions also show synchronized activity during rest. These functional neural interactions are referred to as task-negative networks or RSNs (Fox et al., 2005). So, the resting brain does not turn into an idle state when no acute task is present but rather remains in a state of neuro-electrical and metabolic activation upon intrinsic origin (Rosazza & Minati, 2011). RSNs are suggested to represent spontaneous cognitive processes on the one hand, as well as a function of standby activation of neural pathways typically engaged in habituated tasks on the other hand (Rosazza & Minati, 2011). Upon the association of RSNs with habituation and underlying neurophysiological affordances arising from everyday life, RSNs are suggested to be highly individual and are associated with important functions of the CNS such as memory and consolidation (Stevens et al., 2010).

Although the investigation of task-positive brain networks and their contribution to cognition and sensorimotor tasks is of special interest to understand brain function and dysfunction in both clinical and health-related settings (Fox & Greicius, 2010; Hausman et al., 2020), their interpretation can be biased by interpretative ambiguities such as practice effects or expertise (Fox & Greicius, 2010). Further, the susceptibility of neurophysiological methods to movement artifacts limits the ability to quantify the interaction between neurons during movement (Gorjan et al., 2022). In contrast, modulations of RSNs are less likely to be biased due to confounding factors such as task complexity or cognitive capacity since they are recorded in a neutral, non-experimental situation (Hausman et al., 2020). Further, the RSN approach circumvents the contamination of the recorded neurophysiological data through movement-artifact, since the participant is resting when the neurophysiological data is recorded (Brigadoi et al., 2014; Gorjan et al., 2022). Moreover, RSN recordings require less time compared to task-positive network assessments since they do not rely on the repetitive conduction of experimental tasks or conditions (Hausman et al., 2020). Accordingly, the detection of exercise-induced modulations in brain function based on RSNs may serve as an unbiased and time-efficient paradigm to quantify the modulation of neurophysiological interactions induced by exercise.

The physiological mechanisms underlying the acute modulation of brain function at rest after exercise cessation can be closely related to two mechanisms conceptualized in the reticular-activation-hypofrontality theory (Dietrich & Audiffren, 2011). One mechanism underlying acute changes in RSNs is the transient accumulation of exerkines and neurochemicals in the brain (Basso & Suzuki, 2017). Since the concentration of BDNF, dopamine, or lactate in the CNS remains elevated after exercise cessation, the transient neuroregulatory effects of exercise on synaptic processes outlast the acute duration of exercise. Further, the task-dependent modulations of CBF will particularly lead to transient modulations of oxygenation and exerkine accumulation in brain areas with a recent history of exercise-related activation (MacIntosh et al., 2014). Therefore, recently activated brain networks are more likely to show modulations of activity and connectivity through exerkines after exercise. Because of that, transient changes in RSNs after exercise may represent altered brain function due to transient biochemical modulations of neural ensembles involved in the preceding exercise-induced neural activation patterns.

To track large-scale functional changes in RSNs as a hallmark of the dose-response-relationship between exercise and CNS function, the application of functional neurophysiological methods grants specific insights into modulations of functional integration after exercise. To date, metabolic imaging techniques such as fMRI or fNIRS and electrophysiological techniques such as the EEG are the most frequently used applications in exercise neuroscience research (El-Sayes et al., 2019). The advantage of these methods in comparison to the invasive extraction of blood markers is that they obtain information on the function of the CNS non-invasively. Since each method comes with specific strengths and limitations, the choice of the most suitable neurophysiological method highly relies on the specific exercise neuroscientific research question to be answered (Seidel-Marzi & Ragert, 2020). The metabolic methods provide a good (fNIRS) and excellent (fMRI) spatial resolution for RSN assessment. However, the physiological principle underlying the methods, the neurovascular coupling, quantifies the neural response to changing tasks with a delay of multiple seconds and therefore limits the temporal accuracy of the obtained information (Seidel-Marzi & Ragert, 2020). In contrast, the EEG provides excellent temporal resolution to quantify RSNs, although the non-neural, conductive tissue between the sensors and the nerve cell limits the spatial accuracy of the technique through volume conduction (Mehta & Parasuraman, 2013). Further, the EEG and fNIRS have a limited penetration depth and are restricted to the cortical layers of the brain, while the fMRI can also quantify the activity of subcortical brain areas (Mehta & Parasuraman, 2013). However, the most important downsides of the fMRI compared to the fNIRS and EEG are the immobility and the measurement costs, which restrict its application to clinical investigations in laboratory environments. In contrast, the fNIRS and EEG are portable and more affordable methods that allow for the assessment of RSNs in variable environmental settings, also during movement. However, the assessment of neurophysiological data during movement is still limited due to movement artifacts contaminating the signal and limiting the analysis toward high-intensity whole-body movement (Brigadoi et al., 2014; Gorjan et al., 2022). Taken together, each neurophysiological technique comes with specific up- and downsides. Depending on the specific research question, the aspects of spatial resolution, temporal resolution, portability, and penetration depth might be weighted differently (Seidel-Marzi & Ragert, 2020). An overview of the different methodological features of the three proposed methods can be found in Table 1.

Table 1. Applicability features of preferred neurophysiological techniques in the field of exercise neuroscience.

Method	Physiological principle	Spatial precision	Temporal precision	Portability	Penetration depth
fMRI	*Blood oxygenation level-dependent contrast (BOLD)*	+ + +	+	+	+ + +
fNIRS	*The Near-Infrared light absorption rate of oxygenated blood*	+ +	+ +	+ + +	+
EEG	*Sum signal resulting from excitatory and inhibitory postsynaptic potentials*	+	+ + +	+ + +	+ +

Comparison of application features between functional magnetic resonance imaging (fMRI), functional near-infrared spectroscopy (fNIRS), and electroencephalography (EEG). The count of "+" indicates a ranking of the compared methods concerning the specified feature (Mehta & Parasuraman, 2013).

1.4 Investigating changes in RSNs utilizing the EEG

Several fMRI studies investigating the properties of RSNs before and after acute bouts of exercise support the assumption of transient modulations of brain function after exercise cessation (Won et al., 2021). Depending on the specific approach of the given investigation and the prior chosen brain regions of interest, different RSNs demonstrated exercise-induced modulations. Overall, RSNs associated with sensorimotor processing (Rajab et al., 2014; Ueta et al., 2022), cognitive processing (Schmitt et al., 2019; Weng et al., 2016; L. Zhu et al., 2021), or emotional control (Ge et al., 2021) indicated significant increases in connectivity after a single acute bout of exercise. As reported by Schmitt et al., (2019), intensity is likely to moderate the temporary modulations of RSNs after acute exercise. While low-intensity exercise upregulated the communication within an attention-related RSN, high-intensity exercise upregulated connectivity within an attentional RSN but downregulated synchronous activity within a sensorimotor RSN (Schmitt et al., 2019). A more recent study by Ueta et al. (2021) also provided indications that next to exercise intensity, the mode of exercise may also moderate the acute modulations of RSNs. Comparing an acute session of sensorimotor balance exercise with aerobic walking exercise, fMRI data revealed stronger modulations in sensorimotor RSNs following the bout of exercise with a sensorimotor focus (Ueta et al., 2022). Even though the range of studies investigating exercise-induced changes in large-scale RSNs is still limited, the above-summarized findings hint toward dose-specific modulations of RSNs after exercise mediated by the variables exercise intensity and mode.

Although the RSN approach reduces issues of neurophysiological techniques regarding i) the domain-specificity of the results and ii) the susceptibility of the techniques to motion artifact, evidence on acute changes in RSNs following acute bouts of exercise is limited to fMRI-based investigations. This might be because the degrees of freedom in the portability of fNIRS and EEG rather motivated research to investigate functional brain activity during whole-body movement (Song et al., 2022; Stone et al., 2018). Therefore, RSN investigations in the context of acute exercise remain limited due to fMRI-specific restrictions of i) limited temporal resolution, ii) reduced field applicability through immobility, iii) high application costs and iv) considerable post-exercise preparation times. Considering the requirements of the monitoring of CNS function in exercise raised by Perrey & Besson (2018), a portable technology is required which provides easy-to-interpret information on brain function. Further, a high temporal resolution seems beneficial to match the speed of firing of the neural ensembles contributing to cognition and sensorimotor control (Nordin et al., 2019; Scharfen et al., 2022). While both the fNIRS and EEG overcome the issue of portability, the application of EEG particularly outperforms the fNIRS regarding temporal resolution (Mehta & Parasuraman, 2013). As a result, the EEG became a valuable alternative in RSN research due to its excellent temporal precision and portability (Bastos & Schoffelen, 2016). Consequently, RSN approaches based on the EEG allows for research outside of the lab and the assessment of neurophysiological data closer to the real-world exercise environment (Park et al., 2015). In addition, technological developments such as dry or saltwater electrodes reduce processing times drastically (di Fronso et al., 2019). Further, it is worth noting that comparative studies observed significant associations between reconstructed metabolic fMRI and electrophysiological EEG RSNs (Ebrahimzadeh et al., 2022). Accordingly, the advantages of portability and excellent temporal resolution make the EEG a promising approach for RSN investigations in the field of exercise neuroscience.

Technically, the EEG captures changes in the electrophysiological activity of the brain via electrodes placed on the scalp surface. Because of the conductivity of the tissue in-between the electrode and the firing cortical neurons, electrical potential changes generated inside the brain propagate to the scalp surface and can be quantified by non-invasive surface electrodes. Due to the high sampling frequency of the electrical amplifiers, electrical potential changes can be captured at a high temporal resolution (500 to 1000 Hz) and allow for the investigation of brain activity on a millisecond time scale (Mehta & Parasuraman, 2013). Since the EEG captures neural activity non-invasively and distant from the single nerve cell, the raw data recorded by the single EEG electrode resembles a sum signal of underlying electrical oscillations resulting from both excitatory and inhibitory postsynaptic potentials (Kirschstein & Köhling, 2009). Based on the high temporal resolution of the recorded data and the high density of surface electrode distribution on the scalp, the recorded sum signal can be decomposed according to the characteristics of the recorded oscillations, such as signal amplitude and frequency (Gasser & Molinari, 1996). Therefore, the analysis of the EEG signal allows for conclusions regarding functional changes in the activity of and interactions between the cortical neurons in the electrode subspace (Gasser & Molinari, 1996).

In the analysis of EEG data, two general approaches can be differentiated: the assessment of continuous, spontaneous brain activity and the analysis of cortical activity changes in response to defined events (Gasser & Molinari, 1996). The event-related analysis makes use of the EEG's high temporal resolution and allows for the analysis of oscillation patterns time-locked to a given event. In the context of exercise, these events can be defined as either sensory stimuli presented or the time courses of movement responses (Gasser & Molinari, 1996). However, the domain-specific information makes event-related analysis approaches less suitable for the monitoring of generic dose-response-relationships between exercise and CNS function. In contrast, the analysis of spontaneous oscillations reflects a more general, domain-unspecific analysis of the acute functional properties of the CNS. For continuous analysis, scalp oscillations are analyzed throughout specified time windows concerning frequency and amplitude changes. One the one hand, signal frequencies allow for specifications of the neural populations activated, while signal amplitudes allow for assumptions on the degree of synchronous firings of the specified ensembles in the electrode subspace (Gasser & Molinari, 1996). In the context of exercise science, the EEG power spectrum is typically subdivided into the theta (4-8 Hz), alpha (8-13 Hz), and beta (15-13 Hz) frequency bands (Cheron et al., 2016). Modulations in the different frequency bands are associated with exercise-related neural processes related to sensorimotor integration (theta), task-related inhibition, and gating (alpha) or motor binding (beta) (Cheron et al., 2016). Thus, EEG studies related to exercise have already demonstrated increased activity in the theta, alpha, and beta frequency during the execution of acute bouts of physical exercise such as cycling (Hosang et al., 2022) or sensorimotor exercise such as golfing (S. J. Tan et al., 2019). Further, the continuous analysis of the EEG also provided insights into transient changes in brain function in the resting state after acute exercise (Gramkow et al., 2020; Hosang et al., 2022). To that end, modulations of EEG oscillations reveal information on the altered electrophysiological activity of underlying neural ensembles due to exercise and grant insights into the dose-specific interactions between exercise and brain function.

Apart from the analysis of the electrophysiological activity of underlying regional ensembles of neurons, the EEG also allows for the analysis of cross-cortical communication processes. The analysis of EEG-derived networks bases on the construction of so-called brain graphs. Brain graphs are mathematical representations of cortical networks and allow for the analysis of the topographical properties of these networks (Vecchio et al., 2017). In EEG networks, nodes can either represent the signal of a single EEG channel, the averaged signal within predefined regions of interest, or cortical sources estimated based on processing tools such as the independent component analysis (ICA) (Miljevic et al., 2022). The edges display the functional connections between pairs of nodes and can be estimated as a function of shared information between two signals (Rubinov et al., 2009). Since the EEG signal displays a complex time series of high-resolution electrical oscillations, various approaches allow for a quantification of FC based on statistical relationships between signals such as coherence, correlation, coupling, or synchronization (Imperatori et al., 2019). Depending on the amount of shared information between two signals, the weight or the strength of an edge is computed. According to the distribution and strength of edges across the scalp, the topography of RSN can be inferred. For instance, the distribution and strength of specific edges allow for assumptions on the tendency of the brain toward the two key principles of cortical communication, functional integration and functional segregation (Vecchio et al., 2017). In consequence, the EEG allows for a more particular analysis of the temporal dynamics of brain communication compared to the fMRI in spite of limited spatial accuracy.

In the past decade, changes in RSN organization as a ratio between functional segregation and integration were identified in concussed athletes (Adebimpe et al., 2016), children with benign epilepsy (Kaushal et al., 2019), elderly individuals suffering from Alzheimer´s disease (Vecchio et al., 2022) or adults with major depressive disorder (Sun et al., 2019). Comparing Alzheimer´s disease patients with healthy controls, Vecchio et al. (2022) associated reduced efficiency in the communication of brain signals with the limited capacity of information processing in the populations. Moreover, Kaushal et al. (2019) interpreted increased overall brain connectivity in collegiate football athletes during sub-acute phases of concussion as a dysfunctional over-excitation of the cortex (Kaushal et al., 2019). In the context of exercise, only a few studies applied graph theoretical approaches to reconstruct cortical network dynamics. Due to the high degree of portability of the EEG, researchers tend to rather investigate cortical network dynamics during movement (Gorjan et al., 2022) than during resting conditions. However, the underlying principles of extracting brain networks based on EEG signals remain the same and serve as proof of feasibility to describe brain network dynamics. For instance, Porter et al. (2019) investigated EEG oscillations from an incremental cycling protocol with a concurring cognitive task to investigate exercise-related changes in the brain network topology of the frontal cortex. After gradually increasing both the intensity of the cycling task and the difficulty of the working memory task, a drop in efficiency in the frontal network was observed (Porter et al., 2019). In particular, the theta network indicated strong modulations at severe exercise intensities. Since the behavioral data also indicated a simultaneous drop in cognitive performance, the changes in the theta network were interpreted as an exercise-induced drop in the efficiency of cognition- and attention-related networks. Tamburro et al (2020) also observed intensity-dependent modulations of global network topology throughout an incremental cycling trial. The study findings revealed a quadratic association between intensity and brain function, since global efficiency increased at early to moderate exercise intensities, while no changes were observed at lower and higher exercise intensities (Tamburro et al., 2020). The authors hypothesized that increases in global efficiency may reflect greater alertness of sensorimotor areas following the initiation of exercise. In contrast to the previously mentioned studies, Li et al (2022) investigated network topology in resting conditions before and after a session of exhaustive biceps curl exercises performed until muscle failure. After exercise, the authors observed reduced efficiency in brain networks in the beta frequency band, which are associated with motor control processes (Z. Li et al., 2022). Overall, the above-mentioned findings demonstrate that functional characteristics of electrophysiological brain networks seem modulated by acute bouts of exercise in an intensity-dependent fashion. Thus, the physiological stimuli induced by exercise modulate cross-cortical integration and segregation and these modulations can be quantified by brain graphs using a portable neurophysiological method. In this regard, the transient modulations of cortical RSNs may serve as indicators for the dose-specific modulation of brain function after exercise.

1.5 Rationale

Participation in exercise requires the contribution of different physiological systems to accomplish the required work. A physiological system with a key role in exercise physiology is the CNS because it contributes to the processing of task-relevant sensory information and the generation of motor behavior. However, cross-talks between the CNS and other physiological systems involved in exercise can modulate these neural processes under exercise conditions. One way to explore the interaction between exercise and brain function is the assessment of transient modulations of brain function after exercise cessation due to EEG-derived RSNs. Compared to the investigation of brain function during exercise, the RSN approach is less affected by movement-related artifacts and further offers a domain-unspecific insight into the modulations of brain function.

The modulatory effect of acute exercise on brain function highly relies on the characteristics of the prescribed dose of exercise. Investigations of RSNs using fMRI technology revealed that both exercise intensity and mode could serve as moderators of the acute exercise-induced modulations of brain function. Exercise intensity seems to affect brain function in a non-linear manner since facilitation of brain function is particularly observed at moderate exercise intensities. In contrast, the relationship between exercise mode and modulations of brain function is less clear. However, the sensorimotor demands of exercise may serve as an additional influence on the acute modulations of brain function. Since the CNS is the main instance for the processing of task-relevant sensory information, transient modulations of brain function through exercise can be decisive for sports performance. While exercise doses that facilitate the neural processes underlying sensorimotor control and cognition may improve sports performance, doses that dampen cortical information processing may impair sports performance transiently. Therefore, the investigation of dose-specific modulations of brain function is important to understand complex interactions between physiological systems in exercise physiology. However, CNS measures are barely considered in exercise science research to date.

So far, the immobility and high costs of fMRI restrict RSN research to highly controlled laboratory studies and limit the degrees of freedom regarding exercise protocol prescription. In contrast, the EEG features higher temporal resolution, higher portability, reduced preparation times, and lower measurement costs than the fMRI. The advantages of portability allow EEG research to take place outside of traditional laboratories and consider both quantitative and qualitative exercise variables in more variable and realistic settings. Further, the utilization of a more affordable and applicable neurophysiological method to analyze RSNs would enable more researchers to investigate exercise-induced modulations of brain function in the context of sports and exercise.

Therefore, the opportunity to quantify brain-exercise-interactions due to a portable neurophysiological method with high temporal resolution can contribute to an improved understanding of acute exercise-brain interactions. Once the acute changes in brain function in response to exercise are better understood, longitudinal investigations may also provide complementary insights into the long-term adaptations of the CNS to exercise. In consequence, the integration of the CNS into exercise physiology research may allow for better individualization and prescription of training doses to control and anticipate adaptations of body function and sports performance.

1.6 Objectives

The present thesis aimed to explore the dose-response-relationship between acute exercise and brain function due to the reconstruction of cortical RSNs. In order to increase the applicability of the potential findings and methods in the field of exercise science, a portable neurophysiological assessment was applied utilizing the EEG. In the experimental studies of this thesis, EEG resting states were recorded repeatedly throughout intermittent exercise protocols to reconstruct RSNs based on a graph theoretical approach. The developed exercise protocols allowed for systematic and controlled manipulation of the induced exercise doses concerning the variables intensity and mode. The comparison of RSN organization before and after prescribed bouts of exercise is suggested to provide particular insights into the dose-specific modulations of brain function after exercise. To gain an initial insight into the modulations of EEG-derived RSN organization through exercise, three scientific studies were conducted.

In the first study, an individualized and incremental treadmill protocol was developed to examine acute modulations in RSNs related to the manipulation of exercise intensity. Since exercise intensity has been frequently associated with modulations of brain function, Study I aimed to test the feasibility of the RSN approach in detecting exercise-induced changes in brain function. In the second study, the reliability of the extracted RSN outcomes was analyzed in a week-to-week investigation. The same group of individuals performed a low-intensity bout of exercise twice within one week. The quantification of reliability of the extracted outcomes aimed to provide information on the reproducibility of the RSN reconstruction in repeated measured designs. Finally, Study III explored the modulations of RSN organization induced by different modes of exercise. Therefore, two different endurance exercise modes with matched intensity profiles but different mode-specific demands were compared by employing treadmill running and cross-country (XC) skiing. The study aimed to examine the sensitivity of the proposed approach toward doses of exercise specified by mode. All studies were conducted with healthy young males, while the third study examined changes in RSN organization in highly trained, young athletes. The specific objectives of the studies were defined as follows:

Study I: The major aim of Study I was to examine the effect of exercise intensity on RSN organization quantified by EEG-based graph analysis. In a within-subject design, individuals performed incremental treadmill running with intermittent EEG resting state recordings. Besides the EEG data, physiological outcomes of HR, $B_{La,}$ and BS were recorded to objectively quantify exercise intensity. Therefore, exercise intensity as the most frequently reported moderator of brain function served as the independent variable. The network characteristics derived from the reconstructed RSNs served as dependent variables. The study sample consisted of healthy, young, and active males. Since the EEG-based RSN approach has not been applied previously to analyze acute modulations of brain function through exercise, the initial study of the project aimed to investigate the feasibility of the RSN approach to quantify exercise-brain-interactions.

Study II: The major aim of Study II was to investigate the test–retest-reliability of RSN reconstruction before and after acute bouts of exercise. Therefore, RSNs of the same group of individuals were reconstructed twice within one week. On both occasions, EEG resting states were recorded before exercise and after an acute bout of low-intensity treadmill running. The reliability was calculated based on the intra-individual differences from week to week. The study sample consisted of the same young, active males examined for Study I. The findings were essential for further applications of the RSN approach by giving a specific impression of the reproducibility of the RSN outcomes in repeated measures designs. An understanding of the reliability of neurophysiological markers facilitated the adequate interpretation of acute and chronic modulations of RSN organization induced by exercise.

Study III: The major aim of Study III was to explore the modulatory effect of exercise mode on exercise-induced changes in RSN organization. Therefore, modulations of RSN organization in response to two incremental exercise protocols on an XC skiing treadmill and a running treadmill were compared. The sample consisted of highly trained, young, and male XC skiers. By matching both protocols' exercise intensity, the two prescribed protocols allowed for a specific differentiation of the prescribed exercise doses regarding exercise mode. So, the final study of this thesis aimed to explore the sensitivity of the RSN approach toward the manipulation of the dosing variable mode. The findings of

Study III allowed for specific insights into the modulatory role of exercise intensity and mode in the dose-response-relationship between exercise and brain function.

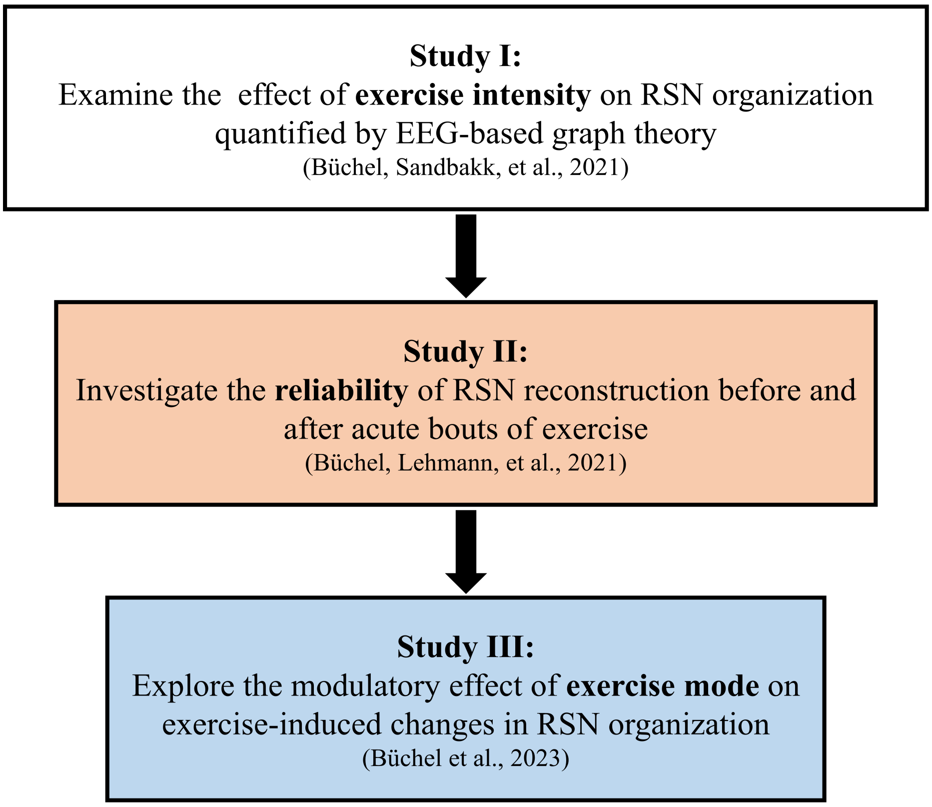

Figure 2. Schematic overview of the objectives of the three included studies.

2 Methods

In the following chapter, the methodological approach chosen for the present thesis will be explained. Therefore, considerations about the chosen samples, the developed exercise protocols, the physiological measures included, as well as the reconstruction of RSNs will be elaborated. Since the thesis aimed to explore the acute exercise-induced modulations of RSN organization assessed by EEG, the common methodological features of the three experimental studies are described in detail. Further, specific differentiations between the three studies will be pointed out. The information on the statistical approaches of the included studies is presented in the methodological sections of the published articles.

2.1 Design

To explore modulations of RSN organization in response to acute bouts of exercise, a within-subject design was chosen. Since both the physiological responses to exercise are highly individual, repeated assessments of the same individuals allowed for paired statistical comparisons that are less affected by inter-individual heterogeneity (Hecksteden et al., 2015). According to evidence that exercise-induced changes in brain functions are modulated by intensity (Porter et al., 2019; Schmitt et al., 2019; Tamburro et al., 2020), the exercise protocols on the treadmill were individualized for each participant. As suggested by Herold et al. (2020), preliminary testing allowed for the assessment of individual aerobic capacity. Each participant performed a ramp protocol until voluntary exhaustion to extract peak oxygen uptake (VO^2_{peak}) as an indicator of aerobic fitness. Thus, intensities were adjusted according to the participants' individual performance capacity. During the actual experimental sessions, EEG data were recorded at six time points: i) before exercise, ii-iv) intermediately after bouts of exercise throughout a graded exercise protocol, v) after cool-down activity and vi) after passive recovery. In addition to the assessment of EEG, physiological internal load outcomes of HR, $B_{La,}$ and Borg Scale (BS) RPE were collected for a further specification of the induced exercise load. For Study I, the protocol was performed on the running treadmill. For Study II, EEG data before exercise and after low-intensity exercise were assessed twice within one week to analyze the reliability of extracted RSN outcomes. Both studies took place at the Sports Medicine Lab of Paderborn University (Germany). Since Study

III aimed to investigate mode-specific modulations in RSNs, two incremental exercise protocols were conducted, one on the running treadmill and one on a bigger treadmill allowing for roller-ski skating. The study was conducted and planned in cooperation with Nord University and the Norwegian University for Technology and Science. It was conducted in the Sports Science Lab of Meråker Videregående Skole in Meråker (Norway).

2.2 Sample

The assessment of exercise-induced changes in brain function is highly relevant to assess brain function and adaptation in various populations, including athletes (Perrey, 2022), children (Möhring et al., 2022), the elderly (Vecchio et al., 2022), or diseased populations such as Alzheimer´s patients (Hausman et al., 2020). Since the present thesis aimed to explore dose-response-relationships between acute exercise and the CNS in the context of sports performance, the studies solely included healthy and exercising adults to reduce confounding effects of age, disease, or fitness (Y. Chang et al., 2012). Further, the thesis exclusively included male individuals. On the one hand, experimental pilots with the used EEG system revealed limited data quality due to electrical bridging in female participants with long and thick hair (Alschuler et al., 2014). Further, the first indications point toward a possible influence of the menstrual cycle on RSNs (Haraguchi et al., 2021). To avoid a possible bias in the explorative analysis of RSNs in a repeated measures design, only male individuals were included. Nevertheless, it is worth noting that future investigations in the field of RSN research need to consider sex-related differences in RSN organization to better individualize both training monitoring of the female athlete as well as subsequent exercise prescription (Bruinvels et al., 2022).
For Studies I and II, recreationally active individuals were investigated. Participants were only included if participated in aerobic exercise such as running at least once to twice a week. Participants were excluded in case they reported any neurophysiological or musculoskeletal disorders. Further, all participants denied any acute trauma on the day of the measurement. All individuals (24.6 ± 3.3 years, 76.0 ± 9.7 kg, 182.1 ± 8.7 cm) performed a ramp protocol to assess VO^2_{peak}, and the average aerobic capacity obtained for the group was 51.63 + 5.6 mmol/l/kg.

For study III, a group of highly trained young cross-country (XC) skiers (20.1 ± .6 years, 74.4 ± 5.6 kg, 178.9 ± 5.5 cm) was tested. Since all individuals competed at national XC skiing races and trained about 15 to 20 hours per week at the time of the investigation, the sample demonstrated a particularly high oxygen uptake (65.3 ± 4.3 mmol/l/kg). Again, all participants included did not suffer from any neurophysiological or musculoskeletal disorder or any acute trauma on the day of the measurement. An athletic, highly trained sample was chosen since the study aimed to compare two different exercise modes. Since technique efficiency influences the degree of energy consumption during complex sports like XC skiing (Ø. Sandbakk et al., 2010), intensity and technical efficiency may interfere in low-trained subjects. Therefore, the selection of highly trained athletes was deemed to avoid potential confounding effects of intensity-technique interferences on associated changes in RSN organization. Further, documentations demonstrate that XC skiers train high amounts of both running and XC skiing throughout the season and underline that the athletes were highly familiar with both endurance modes investigated (Ø. Sandbakk & Holmberg, 2017; Solli et al., 2017; Talsnes et al., 2023; Torvik et al., 2021). This reduced the potential risk of confounding effects through neural efficiency or exercise preferences on the brain outcomes of interest (Brümmer, Schneider, Strüder, et al., 2011).

2.3 Ethics

Before participation in the experiments of the present thesis, each individual signed a written informed consent following the Declaration of Helsinki. Individuals were explicitly informed that they were allowed to withdraw from participation at any given time point of the study. All data assessed during the present study were treated under contemporary considerations of privacy and data security and were saved anonymously on the secure servers of Paderborn University.

For Study I and II, each participant ran through a medical assessment including a health history questionnaire followed by a 12-lead resting electrocardiogram (ECG) screened by a physician of the department before the individual assessment started. The procedures of the study were approved by the local ethics committee of Paderborn University.

For study III, no initial medical investigation was performed before the start of the experiment, since athletes regularly performed incremental exercise protocols throughout the season (Talsnes et al., 2020). The ethics committee of the Norwegian University of Technology and Science approved the procedures of the study.

2.4 Procedures

For the analysis of exercise-induced changes in RSNs, a standardized procedure was chosen, including a pre-assessment of aerobic capacity and an individualized exercise protocol. The initial assessment of aerobic capacity provided information on the individual performance level of each participant. Further, the information on the individuals´ aerobic capacity allowed for standardization and individualization of the exercise protocols. The design of an intermittent protocol with breaks between the single intervals of exercise facilitated the intermittent recording of EEG resting states and the assessment of additional physiological outcomes. In the upcoming sections, a detailed description of the preliminary aerobic assessment, the exercise protocols, and the physiological outcomes assessed will follow.

2.4.1 Preliminary assessment of aerobic capacity

Before the experimental trials, an incremental exercise protocol on the treadmill was performed to assess the individual aerobic capacity of each participant (Howley et al., 1995). The incremental protocol was performed on the same treadmill that was utilized for the subsequent experimental sessions. In Study I, the protocol started with an initial warm-up phase of 5 minutes at a speed of 8 km/h while the incline of the treadmill was set to 1 %. After finishing the warm-up, the incremental period started and the treadmill speed gradually increased by 1 km/h per minute until the participants indicated the termination of the protocol voluntarily. In Study III, a preceding submaximal lactate profile protocol was conducted before the start of the incremental test. For the lactate profile, participants started running at 7 km/ h for 4 minutes. After finishing the stage, B_{La} was measured, and in case of a B_{La} concentration < 4 mmol/l, the running speed was increased by 1 m/h and participants ran for another bout of 4 minutes. The submaximal test was terminated once B_{La} concentration exceeded 4 mmol/l (Talsnes et al., 2020). The speed at the stage before reaching B_{La} of 4 mmol/l was chosen as the speed for the warm-up-phase of the incremental test protocol. As explained in Study I, after the initial warm-up phase of 5 minutes the speed was raised by 1 km/h until participants reached voluntary exhaustion. Due to the higher fitness level of the participants, the incline of the treadmill was set to 10.5 %. For the aerobic assessment in the roller ski skating mode, a similar procedure was chosen. The incremental protocol started with a warm-up-phase for 5 minutes and the initial speed of ~ 12 km/h was derived from the submaximal lactate profile test. The incline of the treadmill was set to 5 % throughout the whole protocol. After finishing the warm-up, the speed was increased by 2 km/h per minute until reaching 20 km/h and by 1 km/h per minute for speeds higher than 20 km/h. The protocol was terminated once participants indicated voluntary exhaustion. During roller ski skating, athletes wore a security belt connected to an emergency switch that stopped the treadmill immediately in case of a sudden fall. For the physiological analysis of aerobic capacity, the internal load was extracted through indirect calorimetry and ECG recording.

For indirect calorimetry, differences in the composition of the inhaled and exhaled air were analyzed based on a breath-by-breath gas exchange analysis. The air was captured through a facemask connected to a calibrated sensor that quantified the composition of the air concerning its oxygen and carbon dioxide saturation. Indirect calorimetry serves as the gold standard for aerobic capacity assessment in sports (Keren et al., 1980) since it allows for the direct quantification of ventilation performance parameters such as the VO^2_{peak}. The VO^2_{peak} quantifies the maximum amount of oxygen the exercising individual can take up per time unit during a prescribed exercise protocol. It relies on two major factors, i) the individual volume of air the participant can exchange in a given time window (ventilation capacity) and ii) the ability of the body's physiological systems to transfer oxygen from the inhaled air into the blood. While the ventilation capacity strongly relies on genetic factors such as body size, lung volume, and sex (Lutfi, 2017), the transfer of oxygen from the air into the blood is highly trainable. For instance, cardiovascular and respiratory adaptations to chronic exercise can increase the efficiency of blood oxygen uptake. Thus, the VO^2_{peak} relative to body weight (in ml/min/kg) serves as a valid outcome to quantify fitness levels in endurance athletes due to its strong association with competitive performance in endurance sports (McLaughlin et al., 2010). In all three studies, VO^2_{peak} was determined as the highest average VO^2 value observed throughout a consecutive 1-min measurement window.

Next to the assessment of VO^2_{peak}, the recording of ECG throughout the protocol allowed for the extraction of individual peak heart rate (HR_{peak}). In all three studies, HR_{peak} was defined as the maximum absolute HR value measured throughout the incremental protocols. The HR_{peak} serves as a valid marker for the maximal capacity of the cardiovascular system and allows for a comparison of cardiovascular load across subjects by interpreting acute HR in relation (%) to the observed HR_{peak} (Achten & Jeukendrup, 2003).

For Study I, the mobile Metalyzer 3B system (Cortex Biophysik, Leipzig, Germany) was used for indirect calorimetry, and the Polar H10 sensor (Polar, Kempele, Finland) assessed ECG throughout the protocol. For study III, the VYNTUS CPX system (Vyaire, Höchberg, Germany) was utilized for indirect calorimetry and the HRM3-SS sensor (Garmin, Kansas, United States) recorded the ECG response.

2.4.2 Exercise protocols

The developed exercise protocol allowed for the investigation of dose-specific modulations of RSN organization in response to acute exercise due to the controlled manipulation of variables intensity (Study I and III) and mode (Study III). An overview of the experimental procedure of the three included studies can be found in Figure 3.

For Study I, the parameter of exercise intensity was manipulated based on the EL parameter of running speed. The chosen mode of exercise was running. Since exercise intensity is defined as the workload in relation to the maximum workload an individual can achieve, the running speed at the time point of maximal oxygen uptake (vVO^2_{peak}) was determined as maximum individual workload (100%). For a clear differentiation between the prescribed intensities, 50, 70, and 90 % of vVO^2_{peak} were selected as speeds corresponding to low, moderate, and high exercise intensities, respectively. For the low (50% vVO^2_{peak}) and moderate (70% vVO^2_{peak}) exercise intensities, a duration of 10 minutes was determined. For high-intensity (90% vVO^2_{peak}), exercise interval was performed until voluntary exhaustion. After the exhaustive stage at 90% vVO^2_{peak}, a first recovery stage at 50 % vVO^2_{peak} for 8 minutes served as a cool-down. Finally, another recovery phase of 10 minutes was included, during which the participants were asked to conduct their individually preferred post-exercise routines for 10 minutes, e.g. stretching or resting.

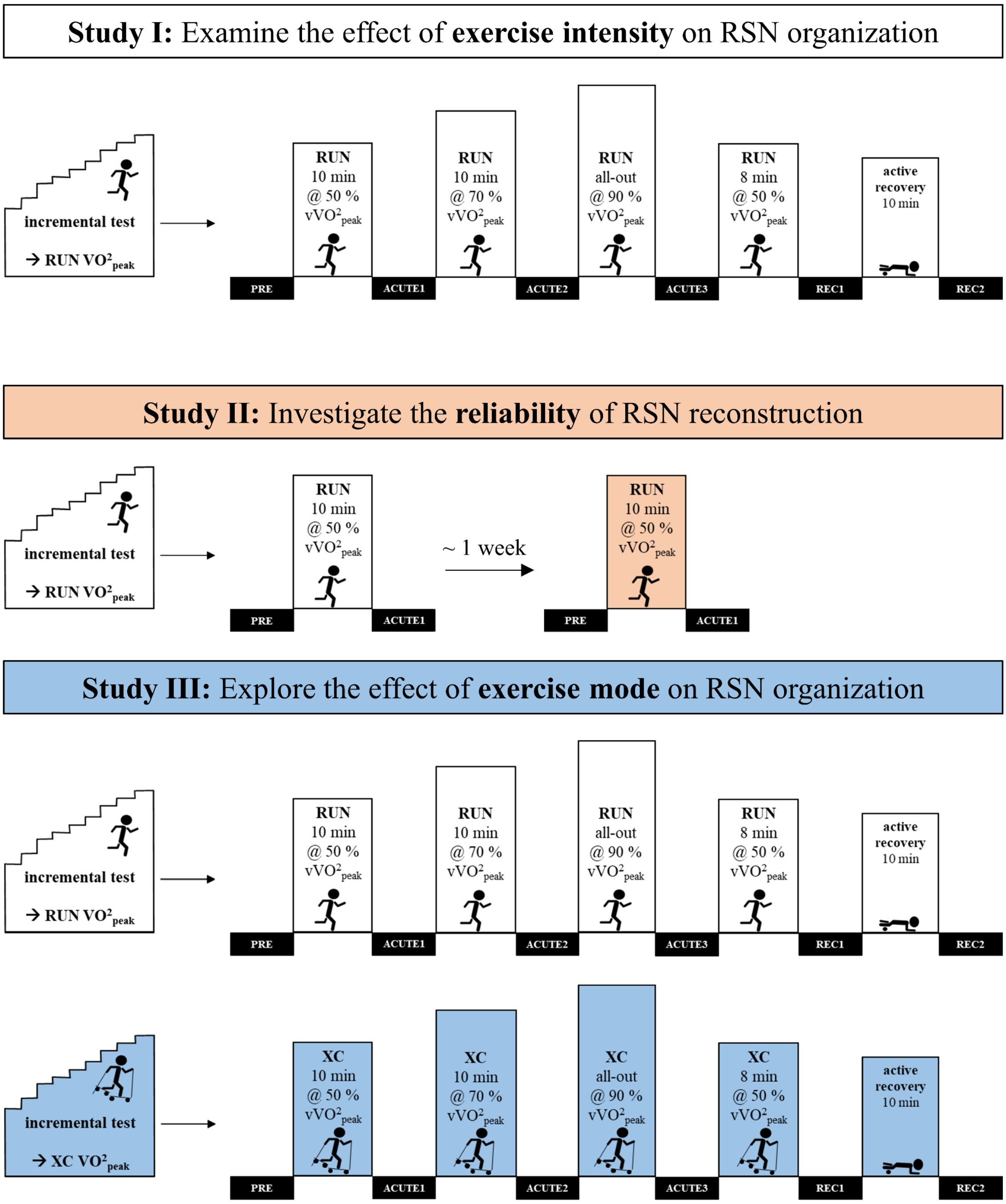

Figure 3. Schematic overview of the study procedures of the three included studies. For each study, participants performed a ramp protocol to assess peak oxygen uptake (VO^2_{peak}). In Study I, participants ran at 50%, 70%, 90%, and 50% of their individual speed at VO^2_{peak}. The black boxes in the figure indicate the time points of (neuro-) physiological assessment (PRE, ACUTE1, ACUTE2, ACUTE3, REG1, and REG2). At each time point, five minutes of electroencephalography resting state data were recorded. Further, heart rate, blood lactate samples, and Borg Scale rating of perceived exertion were assessed repeatedly at the six indicated time points. In Study II, the EEG assessment at PRE and ACUTE 1 were repeated twice within one week. In Study III, all participants performed the incremental protocol explained in Study I in two different exercise modes, running (RUN) and cross-country skiing (XC).

Study II aimed to quantify the reliability of the RSN outcomes. Therefore, RSN outcomes were analyzed before and after an acute bout of exercise twice within one week. To control for an equal exercise load, participants performed 10 minutes of low-intensity exercise based on their individual speed at 50% vVO^2_{peak}. EEG and contextual physiological variables were extracted before (PRE) and after the acute bout of running (POST).

For Study III, both exercise intensity and exercise mode were manipulated. Exercise intensity was manipulated according to the procedures described for Study I. Further, the effect of exercise mode on RSN organization was explored by comparing two endurance modes with different sensorimotor demands. Therefore, the most generic locomotion mode of running was compared to the more complex, but also whole-body endurance exercise mode of XC skiing with high demands on aerobic metabolism (Ø. Sandbakk & Holmberg, 2017). While both locomotion types strongly rely on the propulsion of the legs to generate motion, the upper body muscles play a more significant role in propulsion during XC skiing (Holmberg et al., 2005) For this reason, the inclusion of the upper body increases the sensorimotor demands of the endurance mode from a motor execution perspectives. Further, the integration of poles and skis increases the sensorimotor demands of locomotion by adding the technical elements of arm push and ski gliding (Meyer et al., 2021). Besides, the utilization of poles and skis alters the coordinative demands of the exercise and makes XC skiing rather a four-limb locomotion modality compared to the usual bipedal locomotion in running (Pellegrini et al., 2014). Since there are multiple XC skiing sub-techniques whose utilization in the field depends on e.g. the terrain and incline/ decline of the track, the utilized technique was standardized by instructing the participants to use the G3 technique (Pellegrini et al., 2021). The G3 technique is a skating sub-technique preferred on flat terrain and moderate inclines that is characterized by a symmetrical push of the poles in synchrony with alternating left-and-right leg push-offs (Ø. Sandbakk et al., 2012). Accordingly, the technique requires a precise temporal sequencing of the movements of the upper- and lower body to generate maximal propulsion and is further characterized by longer gliding phases compared to other skating sub-techniques (Meyer et al., 2021). Figure 4 displays an example of the specific movement phases during the G3 movement cycle. Since the experiment was conducted under controlled laboratory conditions, all participants performed roller-ski skating as an indoor and off-snow alternative to XC skiing with matched technical and physiological demands (O. Sandbakk et al., 2011). For a more comprehensive reading throughout the thesis, roller-ski skating will be referred to as XC skiing throughout the upcoming sections of this thesis.

For Studies I and II, the exercise was performed on a motorized running treadmill (h/p/cosmos Pulsar 3p; Traunstein, Germany). For Study III, the protocol was performed on both either a motorized running treadmill (RL 2500E, Rodby, Södertalje, Sweden) or an oversized motorized treadmill allowing for XC skiing (RL 3500L, Rodby, Södertalje, Sweden). All participants were equipped with a pair of body-size fitted poles and used the same pair of roller skis suitable for the G3 skating technique (IDT Sports, Lena, Norway). For Study III, all measurements took place during the competitive phase of the season (October to February), in which only minor changes in the physiological parameters of highly trained XC skiers are observed (Losnegard et al., 2013). Since the testing sessions needed to be fitted into the training and competition schedule of the athletes, ten athletes started with RUN and five athletes started with XC skiing. The time between two EEG measurements was aimed to be less than 2 weeks, but exceeded this time for a few participants due to competition and travel schedule.

2.5 Physiological variables to quantify IL

Throughout the exercise protocol, several internal load parameters were assessed to monitor individual responses to the incremental exercise protocol. This allowed for the quantification of exercise intensity utilizing the average responses of the sample to the prescribed dose of exercise. Since exercise intensity serves as a proxy for acute changes in brain function (Herold et al., 2019), the information on physiological responses is imperative to interpret changes in RSN organization. Further, the assessment of individual internal load data grants insights into inter-individual differences in acute physiological responses to further interpret exercise-induced changes in RSNs.

During the acute bouts of RUN and XC skiing, HR was recorded as the gold-standard of cardiovascular load monitoring. Due to its role in oxygen delivery, HR is a valid indicator of cardiovascular demands and a reliable marker of exercise intensity. Based on the preliminary aerobic assessment, HR was calculated as % HR_{peak}. The analysis of HR in relation to HR_{peak} allowed for a better comparison of exercise responses across subjects due to reasonable inter-individual differences in HR_{peak}.

Before the start of the protocol and immediately after the acute bouts of exercise, a blood sample of 20 µl was taken from the earlobe (Study I) or the fingertip (Study III) calculation of the acute B_{La} concentration as an indicator of metabolic load. The B_{La} concentration provides valuable information on the current metabolic pathways of energy consumption. Since increases in B_{La} are related to increased contributions of anaerobic metabolism, it is a common parameter to assess exercise intensity (Goodwin et al., 2007). Further, blood lactate acts as both an energy supplier but also a neurotransmitter influencing cellular activity in the brain (Hashimoto et al., 2018). Therefore, the assessment of metabolic internal load through B_{La} further helps to understand changes in RSN organization in addition to cardiovascular outcomes

Moreover, RPE was assessed as an indicator of psychophysiological IL. In the present thesis, the BS CR-20 was applied using a visual analog scale that ranged from 6 as a reference for „very easy“ intensity to 20 as an indicator for „maximum exertion“ (Borg & Loellgen, 1998). The BS was assessed during the final minute of the corresponding exercise bout. The RPE method displays a subjective internal load outcome that resembles different inputs emerging to the CNS (Haddad et al., 2017). Thus, several peripheral organs such as muscles, heart, and lungs but also conscious interception provide input and contribute to the perceived exertion (Haddad et al., 2017). The usage of BS as an efficient parameter to assess training intensity is well-established in sports (Impellizzeri et al., 2004). Since not only sensorimotor but also emotional brain networks seem to interact with acute bouts of exercise (Ge et al., 2021), the BS might provide complementary information on the psychophysiological state of the examined individuals.

For this reason, the selection of different internal load parameters allowed for the evaluation of the exercise intensity of the designed protocol from different physiological perspectives. For Study I, the quantification of internal load aimed to quantify the intensity of the prescribed doses of exercise. For Study II, internal load parameters were assessed to describe the reliability of the physiological responses to exercise besides the primary outcomes of interest, the extracted outcomes of RSN organization. For Study III, the assessment of internal load further allowed for the objective quantification of exercise intensity in the two prescribed modes of exercise.

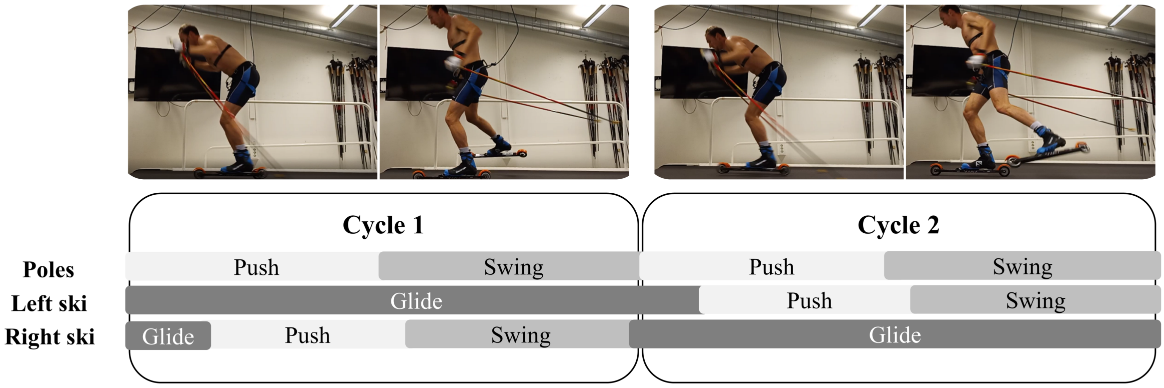

Figure 4. An exemplary overview of the characteristics of the G3 sub-technique. The movement is initiated by a symmetric push-off of the poles and one leg to accelerate the body. The push-phase is followed by a mono pedal gliding phase of the non-pushing leg in a perpendicular direction to the push while both the arms and the pushing leg are swinging. At the end of the swing phase, both skis glide in parallel and the arms move to the front to initiate another symmetric push-off movement of the poles and the alternate leg for further propulsion. A cycle is defined as the movement sequence between two double-pole push-offs. Due to the alternating utilization of one leg for every other cycle in the G3 technique, the athletes move in a zig-zag fashion (Ø. Sandbakk et al., 2015)

2.6 Analysis of resting state network organization

To assess modulations of RSN organization in response to exercise, EEG resting states were recorded repeatedly during the breaks of the intermittent exercise protocols. In contrast to the fMRI as the most frequently used technology to assess RSNs so far, the EEG is a portable method that offers the measurement of cortical function in human sports performance labs, but also in the field (M. Chang et al., 2022). In the present study, a portable EEG system allowed for neurophysiological recordings in exercise performance laboratories. Therefore, the acute effects of exercise intensity and mode on RSN modulations were explored without moving the participants out of the exercise environment. In Figure 3, the time points of the intermittent EEG recordings (PRE, ACUTE1, ACUTE2, ACUTE3, REG1, REG2) throughout the protocols in Study I, II, and III are depicted through the black boxes in the figure. The methodological measures for the recording and processing of the EEG data, the computation of functional connectivity, and the reconstruction of RSNs based on a graph theoretical approach will be specified in the upcoming chapter.

2.6.1 EEG resting state recording

EEG oscillations were recorded by applying a cap of 64 passive wet silver chloride (Ag/AgCl) electrodes (RNET, BrainProducts, Germany) connected to a wireless transmission system that transferred the EEG data to a computer via Bluetooth (LiveAmp, BrainProducts, Germany). The electrode cap was soaked into a potassium chloride electrolyte solution before the measurement and created contact with the scalp surface via soaked saltwater sponges. The electrodes were fitted to the participants' heads according to the international 10-20 system (Klem et al., 1999) using tight-fitting, size-adjustable silicone caps. Before starting the EEG recording, impedances were reduced to < 50 kΩ for all electrodes. Due to the reduced preparation times for saltwater-based electrode systems, the RSN assessment started within three to six minutes after the cessation of the bout of exercise. Therefore, the system outperformed gel-based electrodes for the analysis of acute exercise-induced changes in RSNs, since the time between exercise cessation and neurophysiological recording might be an important aspect to consider when analyzing acute modulations of brain function after exercise (Basso & Suzuki, 2017).

During the experimental sessions, EEG data was recorded in a sitting position for five minutes in human performance laboratories. Participants were instructed to keep their eyes open throughout the whole recording, as eyes closed measurements may induce changes in RSN organization (Yan et al., 2009). Since wearing an EEG cap while running and XC skating at high intensities is uncomfortable and may lead to shifts in the electrode position, the EEG cap was applied to the participant's head before each recording and was removed again after finishing the five minutes of EEG recording. During the measurement, individuals were asked to relax, stay quiet, and avoid talking and intense movement. The EEG raw data were recorded at a sampling rate of 500 Hz. The electrode at FCz served as an online reference and the electrode at the AFz position served as an electrical ground. An example of the experimental set-up of the EEG assessment is provided in Figure 5.

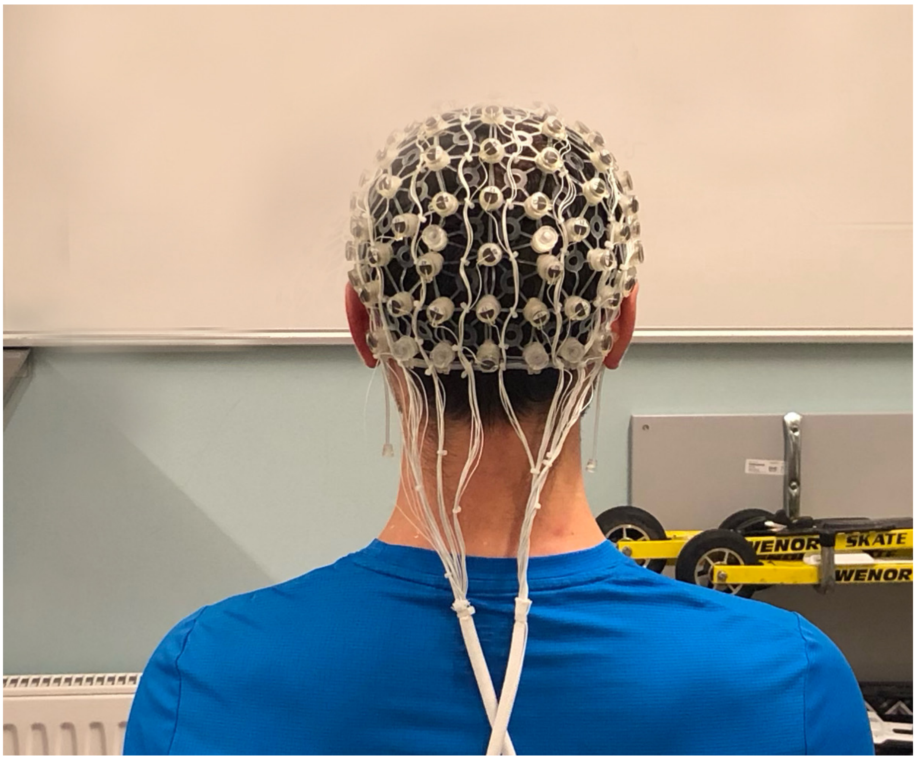

Figure 5. Example of resting state measurement situation from Study III. During the assessment of electroencephalography (EEG) data from 64 wet electrodes (RNET, Brain Products, Germany), participants were sitting in the laboratory for five minutes. Participants were asked to relax, but to keep their eyes open throughout the measurement.

2.6.2 EEG data processing

The EEG signal displays a sum signal of the underlying electrophysiological phenomena since the electrical potential is recorded by electrodes placed on the scalp surface. On the one hand, the billions of neurons in the electrode subspace continuously generate electrical potentials which propagate to the scalp surface. Moreover, the electrodes placed on the scalp surface also record electrical potential changes from other, non-cortical sources such as cardiac, ocular, or muscular activity and are further susceptible to movement-induced artifacts. Therefore, it is crucial to decompose the recorded signal and to get rid of non-brain contributions before analyzing potential exercise-induced modulations of the electro cortical activity.

For all included studies, the EEG raw data was processed according to a series of data analysis steps. The EEG processing aimed to minimize the contamination of the EEG signal due to non-cortical electrical sources. Ergo, two potential types of non-cortical signal sources were targeted: those stemming from non-physiological sources, e.g. electrode pops, and those stemming from physiological sources, e.g. electro ocular or electro-muscular activity. The processing of the EEG data is a stepwise and dynamic approach and specific configurations of single steps need to be adjusted according to the intended analytical approach (Klug et al., 2022). For the present thesis, RSN organization was extracted from data on the channel level. Therefore, the processing required a careful balance between the removal of non-cortical parts and the maintenance of as much cortical data as possible. Since cortical and non-cortical partitions of the EEG signal can share similar characteristics such as frequencies and amplitudes, careful decisions were required. Since common guidelines for EEG network analysis are still lacking (Miljevic et al., 2022), methodological decisions were made based on recommendations from methodological publications in the field of EEG network analysis.

The processing was performed using the EEGLAB open-source toolbox (Delorme and Makeig, 2004) for the MATLAB software (vR2015b, Mathworks Inc., Natick, USA). For standardization and efficiency, all steps were run through customized scripts. First, sinusoidal line noise at the frequencies of 50 and 100 Hz was removed from the raw data using the CleanLine plugin (Mullen, 2011) followed by a basic finite impulse response band-pass filter with a high-pass filter set at 3 Hz and a low-pass filter set at 30 Hz. The band pass filtering of the data removed contents of the data that fell out of the range of the relevant frequency bands including the theta (4-8 Hz), alpha (8-13 Hz), and beta (13 to 25 Hz) oscillations. To reduce the amount of data and processing times, the sampling rate was down sampled from 500 to 256 Hz. (Shannon, 1949). After down sampling, an automatic flat-line channel rejection was applied based on the clean_rawdata plugin (Miyakoshi & Kothe, 2014). During this step, channels demonstrating consecutive periods of zero-values for a continuous period of > 5 seconds were removed from the dataset. In the following step, the data was referenced to the common average. For average referencing, the average signal of all channels was subtracted from each channel to avoid the effects of non-stereotype fluctuations of the online-reference FCz on the recorded data. In the course of re-referencing to common average, FCz was reconstructed in order to add an additional channel to the EEG recording as the negated new reference. Following average referencing, data were checked for electrical bridges using the eBridge tool (Alschuler et al., 2014), and channels involved in electrical bridges were removed from the dataset.

The next processing step targeted the removal of non-stereotypical artifacts. Therefore, the technique of artifact subspace reconstruction (ASR) was applied using the clean_rawdata plugin (Plechawska-Wojcik et al., 2019). The ASR is a technique that identifies deviations of the EEG signal from a reference time window – the calibration data – concerning a predefined acceptable threshold of data variance (Plechawska-Wojcik et al., 2019). According to a previous investigation, the cut-off parameter for the identification of contaminated fragments was set to $k = 10$, as stated to perform best in resting data (Anders et al., 2020). The first 180 seconds of the recording served as calibration data for the ASR. Therefore, data fragments that differed k times from the characteristics of the calibration data – e.g. due to atypical amplitudes and/ or frequencies - were identified and reconstructed based on a mixing matrix based on the calibration data. Accordingly, the application of the ASR allowed for the cleaning of the recorded EEG signal without big data losses and is a promising approach for short EEG recordings (Plechawska-Wojcik et al., 2019). For Study III, the calibration period was further inspected for large-scale non-stereotype artifacts before running the ASR to increase the quality of the calibration data. After the application of the ASR, all rejected channels were interpolated using the spherical interpolation method (Klug et al., 2022; Klug & Gramann, 2021).

In the next step, stereotypical, non-cortical electrical sources were removed from the EEG data. Therefore, the data were decomposed into maximally independent components by applying the adaptive mixture independent component analysis (AMICA) algorithm (Palmer et al., 2011). The AMICA is a processing algorithm that decomposes the linear mixed data of n channels into n spatially, temporally and functionally independent sources, further referred to as independent components (ICs). Given the specificities of the phase oscillations, signal amplitudes, and the spatial location of the different stereotypical components contributing to the sum signal, the AMICA allows for a differentiation between ICs potentially stemming from cortical, physiological (cardiac, ocular, muscular), and non-physiological (e.g. line-noise or channel-noise) sources. An experienced investigator inspected the ICs derived from AMICA for each dataset and assigned them to the categories “brain”, “non-brain” and “mixed”. The classifications of ICs suggested by the tool ICLabel (Pion-Tonachini et al., 2019) were used to support decision-making (Klug et al., 2022). Finally, all components labeled as “non-brain” were subtracted to remove clear non-cortical partitions from the EEG signal. The procedure was the same for all three studies of the present thesis.

As a final step before FC analysis, the data were segmented into epochs. Based on previous investigations from Fraschini et al. (2016), epochs of eight seconds were selected since these were reported to provide the most stable network metrics (Fraschini et al., 2016). The increased variation of the data in longer data epochs was suggested to increase the reliability of FC compared to shorter epochs (Fraschini et al., 2016). Further, an epoch-overlap of four seconds was chosen to double the number of epochs each analyzed sample point contributed to. According to Allen et al. (2004), a window overlap avoids the position of a given sample point in the extracted epoch and affects analytical outcomes (Allen et al., 2004). For Studies I and II, the first 50 epochs were chosen for network analysis. For study III, the first 40 epochs were used for analysis. Due to the pre-cleaning of the baseline window for ASR, the overall amount of data points was reduced, so that for a few subjects less than 50 epochs of 8 consecutive seconds remained after processing.

2.6.3 Functional Connectivity estimation

Following the careful processing and the removal of non-cortical partitions from the data, FC between all possible pairs of channels was calculated for the epoched EEG data. The calculation of FC between the recorded channels is fundamental for later RSN analysis since the estimated FC values display the edges between the pairs of nodes in the reconstructed RSN. The FC between a pair of EEG signals is a function of the mathematical interaction of signal oscillations and can be quantified by a variety of metrics and algorithms (Wang et al., 2014). Among these metrics, all approaches share the principle assumption that two signals interact when they demonstrate patterns of phase synchronization (Wang et al., 2014).

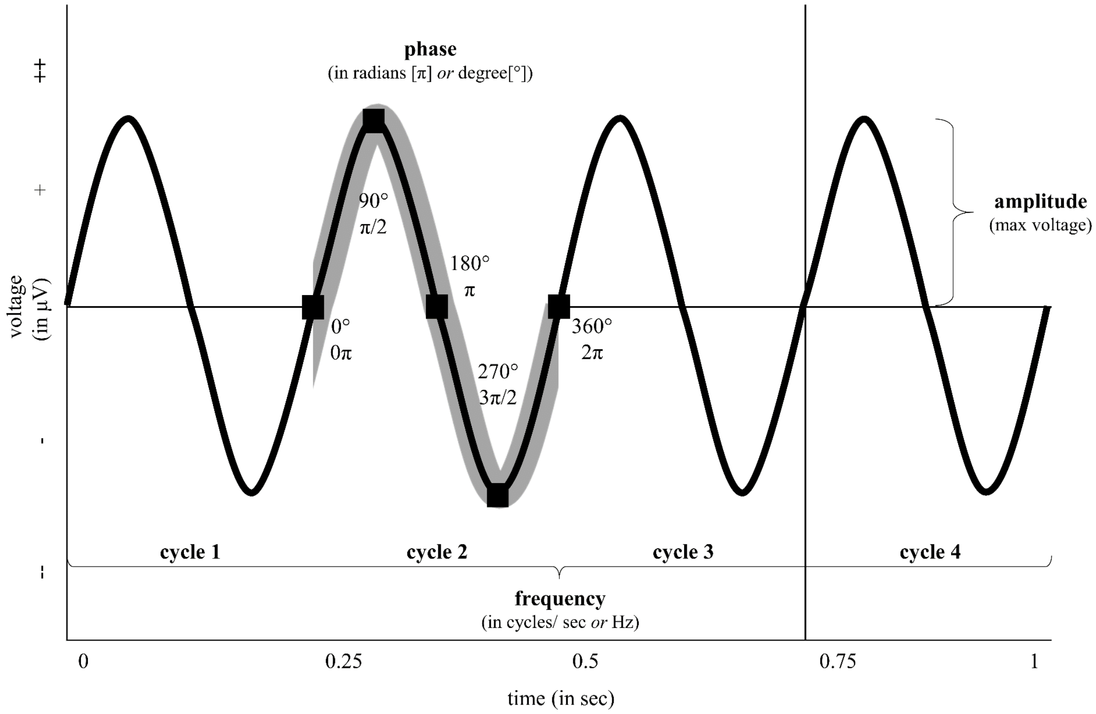

Figure 6. Overview of the three main characteristics of the oscillatory EEG signal. The oscillatory signals of the EEG display a sine wave oscillating around a zero-point. The maximal voltage change of the EEG is referred to as the amplitude or signal power. The oscillation period of one positive and negative deflection peak is referred to as a cycle and resembles 360 °. Within a cycle, the actual position of the signal is referred to as a phase. The phase of the signal can be quantified in ° or radians (π) and describes the timing of the signal. The total number of cycles within a second quantified the frequency or the speed of the oscillation. This figure is modified from Ladouce (2018).

The phase is one of the three features of an oscillatory wave and characterizes the timing of the signal throughout the oscillation cycle (Ladouce, 2018). Within one oscillation cycle, the signal will reach maximal positive and negative peaks, also described as the amplitude or the power of the oscillation. Finally, the number of cycles per second is referred to as the oscillation frequency and characterizes the rate at which an oscillation appears. While amplitudes and frequencies are particularly interesting for the analysis of the EEG power spectrum, the FC approach analyzes the synchrony of the phases of two signals. A schematic overview of the oscillation characteristics of the EEG signal can be found in Figure 6.

For the present thesis, the weighted Phase-Lag-Index (wPLI) was selected for FC computation. The wPLI quantifies the asymmetry in the distribution of phase differences and is based on the instantaneous phases of two time-series. The wPLI is less sensitive to noise and volume conduction compared to other FC metrics (Vinck et al., 2011). Since the channel-based analysis of EEG signals in the present study may increase the likelihood that volume-conduction and noise affect FC, the computation of wPLI likely avoids spurious connections between channels. Further, the exercise-induced increases in power across frequencies (Hosang et al., 2022) are less likely to affect wPLI-based FC estimations given their reduced sensitivity to changing signal amplitudes (Vinck et al., 2011). The wPLI was calculated according to the formula suggested by Vinck et al (2011). In the formula below, *imag* $(S_{xy,t})$ displays the imaginary part of the cross-spectrum of two given signals x(t) and y(t) at a given time point t. The imaginary part of the cross-spectrum hereby describes a complex function of the coherence of the phases between two given time series that cannot be increased due to issues arising from volume conduction (Nolte et al., 2004)As an extension of the original Phase-Lag-Index, the wPLI further weighs the signs of the imaginary part of the cross-spectrum against the imaginary part of the cross-spectrum and therefore weighs the association of two signals to the part of the association less-affected by volume conduction (Vinck et al., 2011)

$$wPLI = \frac{\sum_{t=1}^{n} \left| imag\ (S_{xy,t}) \right| sgn(imag\ (S_{xy,t}))}{\sum_{t=1}^{n} \left| imag\ (S_{xy,t}) \right|}$$

The epoched data was imported to the BrainWave software (Version 0.9.152.12.26, C. J. Stam; available at http://home.kpn.nl/stam7883/brainwave.html) and the wPLI was computed on the channel-level for each possible combination of electrode pairs for each epoch. This resulted in 50 (Study I and II) and 40 (Study III) 65-by-65 grids for each participant and each condition, respectively. The wPLI analysis reveals FC measures ranging between 0 and 1, with 1 representing the highest possible and 0 the lowest possible degree of FC (Vinck et al., 2011). The wPLI was calculated for epochs band-pass filtered in three frequency bands of interest, resembling theta (5 to 8 Hz), alpha-1 (8 to 10.5 Hz), and alpha-2 (10.5 to 13 Hz). For Study II, the beta-1 (13 to 20 Hz) and beta-2 (20 to 30 Hz) oscillations were also included in the analysis. The surrounding bands of delta (1 to 4 Hz) and gamma (30 to 80 Hz) were not taken into account since they were affected by the filtering applied during data preprocessing and are also likely to be affected by eye- and muscle-related signal partitions (Hagemann & Naumann, 2001; Whitham et al., 2007).

2.6.4 Reconstruction of RSN organization

To reconstruct RSNs and analyze modulations of brain functions concerning the cortical key strategies of functional segregation and integration, brain graphs were computed based on the extracted EEG epochs. In general, a graph serves as a mathematical reconstruction of a complex system and quantifies the interaction of the included components (Diestel, 2006). In the context of neuroscience, a graph represents a matrix of functionally interacting brain regions (Vecchio et al., 2020). Therefore, brain graphs provide promising insights into cortical segregation and integration as designated key principles of brain function (Fox et al., 2005).

To reconstruct brain graphs, the generated FC matrices were imported to the MATLAB-based Brain Connectivity Toolbox (Rubinov & Sporns, 2010). For the RSN reconstruction, each recorded scalp signal was defined as a network node and the computed wPLI value between two signals was defined as the edge between the two nodes. Based on the nodes and edges, weighted and undirected graphs were reconstructed in which the edge between a given pair of nodes served as an indicator of the weight of the given connection. Once reconstructing an initial weighted network approach, thresholds can be set to reduce the number of edges included in the graph. The degree of density thresholds is linearly related to the strength of global graph outcomes and needs to be standardized across repeated measures (Adamovich et al., 2022). However, the thresholding of density is likely to bias the likelihood of specific connections contributing to a network. In particular, the authors demonstrated that density thresholding of a graph reduces the likelihood of frontal nodes to be represented in the graph (Adamovich et al., 2022)a. Due to the explorative character of the thesis, no threshold was selected to maintain all possible connections in the data and to prevent a regional bias. To ensure comparability of network measures across the participants, the connectivity matrices were normalized by bounding all wPLI values to a range of 0 to 1 based on the rank of the maximal and minimum wPLI value per participant (Ciccarelli et al., 2019; Mehraram et al., 2020).

Based on the weighted graphs, global graph measures were computed, including the clustering coefficient (CC), the characteristic path length (PL), and the small world index (SWI). The CC describes the tendency of a network to create local triangles. It is an indicator of functional segregation since it reflects the tendency of the RSN toward clustered connectivity around individual nodes (Rubinov & Sporns, 2010). For the present study, the global CC was calculated as the mean CC of every single node of the weighted graph (Onnela et al., 2005).

$$CC = \frac{1}{n}\sum_{i \in N} \frac{2t_i^w}{k_i(k_i - 1)}$$

The PL is an indicator of cortical integration since the length of a path estimates the potential of functional integration across the cortex (Rubinov & Sporns, 2010). The PL is defined as the average shortest path length of a given node and is inversely related to the potential of a given node to exchange information across the cortex. Again, the global PL was computed as the PL of every single node of the weighted graph (Rubinov & Sporns, 2010).

$$PL = \frac{1}{n}\sum_{i \in N} \frac{\sum_{i \in N, j \neq i} d_{ij}^w}{n - 1}$$

In the formulas above, *N* describes the set of all nodes, *n* is the number of nodes, and (*i,j*) displays the connection between two nodes *i* and *j*. Further, *w* is defined as the normalized weight of a connection between two nodes as indexed by the normalized wPLI. To compute the CC, *t* is required as the weighted geometric mean of the triangles around a node and k as the number of links connected to a node. For the calculation of PL, *d* displays the shortest weighted path length between two nodes (Rubinov & Sporns, 2010). Both CC and PL were analyzed as mean values of the 50 (Study I & II) or 40 (Study III) epochs generated per condition and frequency band. As global RSN measures, CC and PL were computed as the mean values of all channels across the scalp.

Based on the calculation of CC and PL, the SWI was calculated and describes the relation between functional segregation and integration and assumes that the efficiency of information exchange is the highest when a network shows few long connections (low integration) and many short connections (high segregation). In this network configuration, information needs – on average – fewer steps to travel from any node of the network to another. Therefore, it differentiates from so-called random networks and so-called regular networks, which are characterized by high clustering and long path length and few clustering and low path length, respectively (Vecchio et al., 2017). An example of differences in the network topology of random, regular, and small-world networks can be found in Figure 8.

The SWI was calculated as the ratio between normalized CC and normalized PL in the given frequency bands of theta, alpha-1, and alpha-2 (Vecchio et al., 2017).

$$SWI = \frac{norm\ CC}{norm\ PL}$$

To normalize CC and PL, the individual value per condition was divided by the mean obtained from the average values of each parameter per EEG frequency bands of each subject and each condition (Vecchio et al., 2017). Since weighted graphs were investigated, normalization of data against surrogate random networks could not be done (Vecchio et al., 2017).

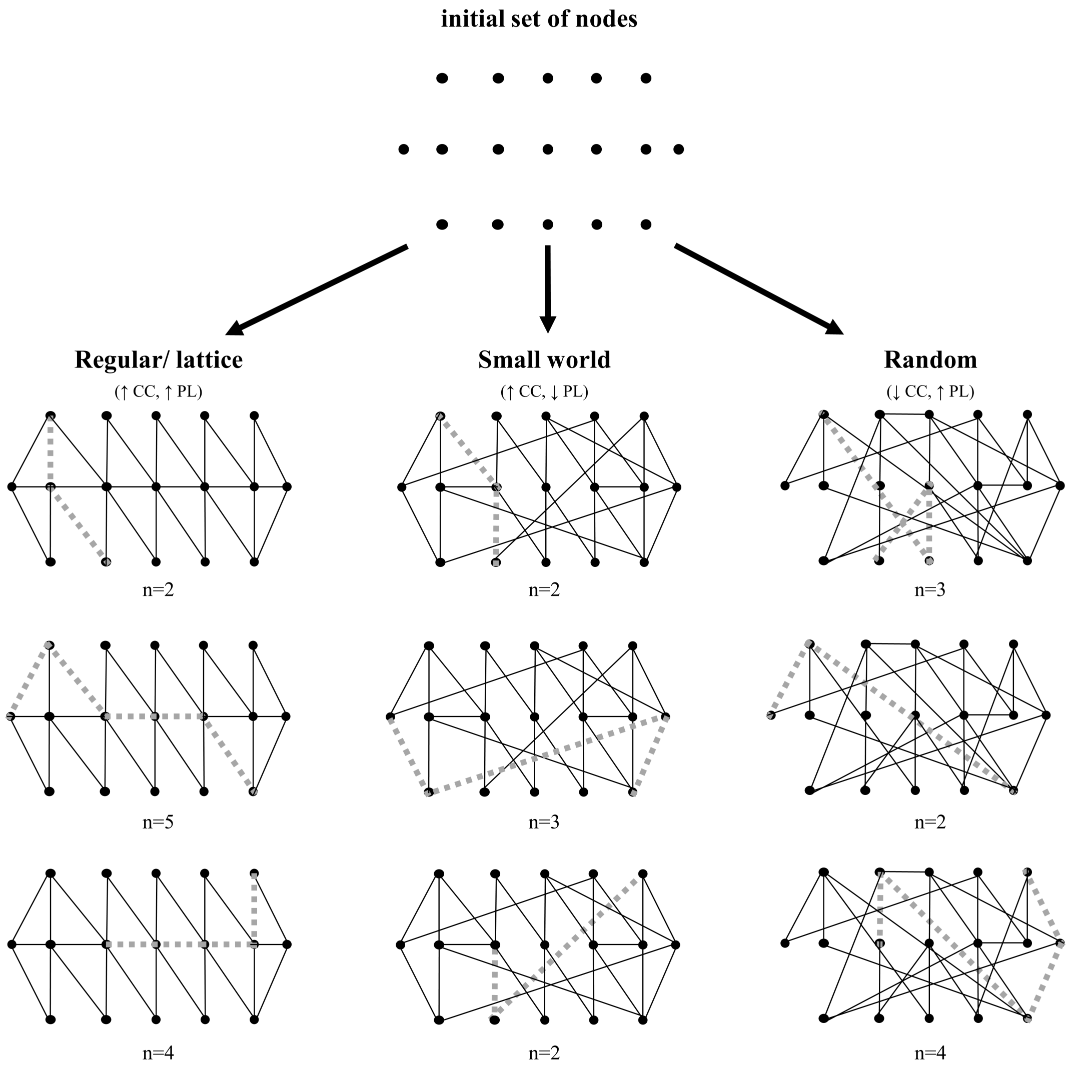

Figure 7. Comparison of topographic differences between network configurations. The network topologies differ regarding their balance between cortical segregation (e.g. indicated by the clustering coefficient [CC]) and cortical integration (e.g. indicated by the characteristic path length [PL]). Regular networks typically demonstrate high CC and high PL, while random networks demonstrate low CC and high PL. As an intermediate network type, small-world networks show high CC and low PL. On average, the information requires the lowest number of steps to travel across the network in small-world configurations. Grey dashed lines indicate an exemplary path between the same two pairs of nodes in three network types. Due to the specific topology, information needs on average fewer steps (n) to travel across the cortex in small-world networks.

3 Results

In the following section, the results of the three included studies will be briefly described concerning the stated main objectives. Therefore, a selective insight into the study findings will be provided. The figures presented were custom-build for the present thesis. The detailed results of the three studies including statistics and secondary analyses can be found in the original manuscripts.

3.1 Study I: Exploring intensity-dependent modulations in EEG resting-state network efficiency induced by exercise (Büchel, Sandbakk, et al., 2021)

The initial study of this project aimed to examine exercise-induced modulations of RSN organization with regard to the manipulations of exercise intensity. Therefore, resting state EEG data were recorded before and throughout an intermittent and incremental exercise protocol on the treadmill. Since the study aimed to identify modulations of RSN organization in response to different intensities, intermittent bouts of exercise at an individualized speed of 50, 70, and 90% vVO^2_{peak} were performed. Next to the EEG resting states, physiological markers of internal load were monitored utilizing HR, B_{La}, and BS.

Based on the assessed markers of IL, a gradual increase in exercise intensities was demonstrated for all assessed parameters. All parameters reached a maximum after 90% vVO^2_{peak}. The intensity of the exercise bout was characterized by an HR of 90.3 ± 3.6 % HR_{peak}, a BS of 18.9 ± 0.6 at the BS CR6-20 scale, and a B_{La} concentration of 7.9 ± 2.1 mmol/l. Further, the statistical analysis of RSN organization revealed intensity-dependent modulations in the efficiency of the theta network (4-8 Hz) throughout the incremental exercise protocol. Particularly after the most intense bout of exercise at 90% vVO^2_{peak}, RSN organization was significantly modulated, as indicated by reduced SWI and CC in the theta frequency band ($p<.05$). In the alpha-1 and alpha-2 frequency band, no systematic modulations in network efficiency were observed. An overview of the main findings including the physiological response and the modulations in RSN organization in the theta band can be found in Figure 8.

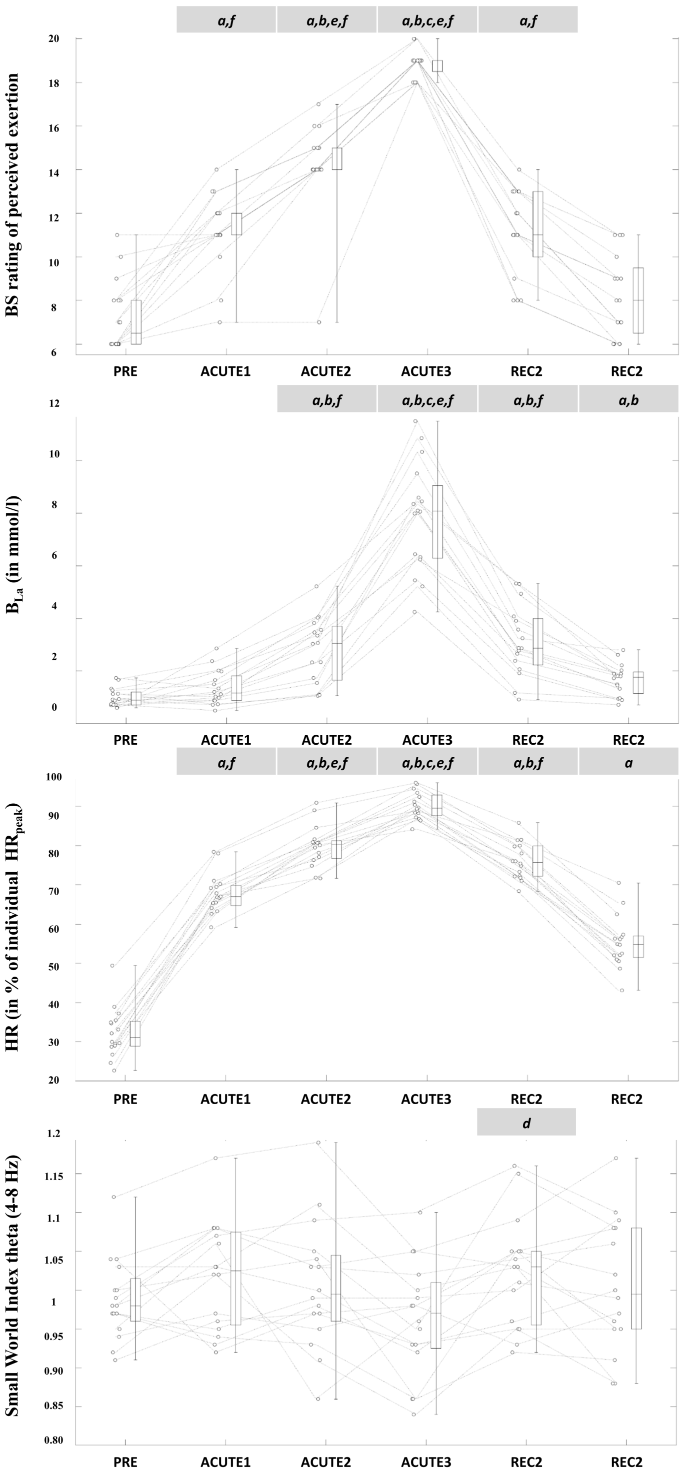

Figure 8. Main findings on physiological and neurophysiological outcomes from Study I. ANOVA revealed a modulatory effect of exercise intensity on physiological outcome parameters and RSN organization in the theta (4-8 Hz) frequency band. Main-effects of exercise intensity ($p<.05$) were observed for i) Borg scale rating of perceived exertion (BS, first panel), ii) blood lactate concentration (B_{La}, second panel), iii) heart rate during exercise (HR, third panel) as well as iii) EEG-derived small-world index in the theta frequency (SWI, fourth panel). Significant differences between conditions ($p<.05$) revealed by post-hoc analysis are indicated in the grey boxes above each panel as follows: *a* = significantly higher than PRE, *b* = significantly higher than ACUTE1, *c* = significantly higher than ACUTE2, *d* = significantly higher than ACUTE3, *e* = significantly higher than REC1, *f* = significantly higher than REC2.

3.2 Study II: EEG-derived brain graphs are reliable measures for exploring exercise-induced changes in brain networks (Büchel, Lehmann, Sandbakk, et al., 2021)

After exploring the potential effects of acute bouts of exercise on EEG-derived RSN organization in Study I, the second study of this thesis aimed to investigate the intra-individual test–retest reliability of the RSN outcomes. Therefore, RSNs were reconstructed based on two EEG resting state recordings, i) a recording exercise (PRE) and ii) a recording after low-intensity exercise on the treadmill at 50% vVO^2_{peak} (POST) which corresponded to ACUTE 1 of Study I. In order to quantify week-to-week reliability, the participants were tested twice within one week. For the analysis of the reliability of the RSN outcomes, Intraclass-Correlation-Coefficient (ICC) was calculated as a measure of relative reliability, and the Coefficient of Variation (CoV) was calculated as an indicator of absolute reliability. ICC and CoV were computed for all physiological outcomes as well as the extracted RSN outcomes, the CC, the PL, and the SWI. The frequency bands of interest were the theta, alpha-1 and alpha-2, beta-1, and beta-2 bands. For the interpretation of ICC values, 0.4, 0.6, and 0.75 were chosen as benchmarks for moderate, good, and excellent relative reliability. For absolute reliability, CoV values < 5 % were rated as good, values < 10 % were rated as moderate, and values > 10 % were rated as poor (Hopkins, 2000).

The reliability analysis of the internal load parameters demonstrated good to excellent reliability for B_{La} based on ICC values $\geq$ 0.6. For BS and HR, relative reliability was poor and moderate, respectively. Absolute reliability analysis revealed moderate absolute reliability for all analyzed internal load outcomes (CoV values > 5 %). For the extracted RSN outcomes, the results revealed ICC values ranging from poor to good at PRE, but good to excellent at POST. In particular, RSN outcomes extracted in the theta and beta-2 frequency bands demonstrated poor-to-moderate relative reliability at PRE, while RSN outcomes in the alpha-1, alpha-2, and beta-1 frequencies demonstrated good-to-excellent reliability. For absolute reliability, particular outcomes in the alpha-1 (SWI PRE & POST), alpha-2 (SWI PRE), beta-1 (SWI PRE), and beta-2 (SWI PRE & POST) frequencies exceeded the threshold of CoV > 5 %. All remaining outcomes demonstrated good absolute reliability (CoV < 5%). An overview of the reliability results for the theta, alpha-1, and alpha-2 frequencies can be found in Table 2.

Further, the effect of acute exercise on the reliability of RSN outcomes was investigated by resampling the original sample of ICC values k= 1000 times by applying bootstrap analysis(Di Plinio, 2022). Following an effect size estimation on the difference between the resampled distributions, improved reliability of RSN outcomes at POST compared to PRE was observed for all frequency bands except for the beta-2 frequency. The raincloud plots presented in Figure 9 provide a visualization of the resampled distributions of the ICC values at PRE and POST for the theta, alpha-1, and alpha-2 frequency.

			Relative reliability			**Absolute reliability**		
			ICC	**LB**	**UB**	**CoV**	**LB**	**UB**
Theta (4-8 Hz)	**CC**	**PRE**	0.44	-0.02	0.76	2.94	3.97	1.93
		POST	0.62	0.16	0.86	3.22	4.78	1.99
	PL	**PRE**	0.27	-0.13	0.64	1.82	2.26	1.27
		POST	0.70	0.30	0.89	1.40	2.14	0.85
	SWI	**PRE**	0.38	-0.07	0.73	4.65	6.12	3.09
		POST	0.65	0.21	0.87	4.55	6.83	2.79
alpha-1 (8-10.5 Hz)	**CC**	**PRE**	0.87	0.61	0.96	3.79	6.63	2.18
		POST	0.92	0.79	0.97	3.28	5.42	1.93
	PL	**PRE**	0.86	0.64	0.95	2.80	4.49	1.67
		POST	0.89	0.72	0.96	2.65	4.33	1.57
	SWI	**PRE**	0.88	0.65	0.96	6.66	11.21	3.89
		POST	0.91	0.77	0.97	6.26	10.23	3.70
alpha-2 (10.5-13 Hz)	**CC**	**PRE**	0.68	0.28	0.88	3.19	4.81	1.95
		POST	0.84	0.59	0.94	2.57	4.11	1.53
	PL	**PRE**	0.57	0.11	0.83	2.46	3.53	1.54
		POST	0.73	0.36	0.90	2.07	3.21	1.25
	SWI	**PRE**	0.64	0.22	0.86	5.52	8.17	3.41
		POST	0.82	0.55	0.94	4.42	7.06	2.63

Data were obtained before (PRE) and after (POST) low-intensity exercise on the treadmill twice within one week. For RSN analysis, clustering coefficient (CC), characteristic path length (PL), and small-world index (SWI) were calculated. As measures of relative and absolute reliability, Intraclass-Correlation-Coefficients (ICC), as well as Coefficient of Variation (CoV), are provided including lower (LB) and upper bound (UB) of the 95% confidence interval, respectively

Table 2. Overview of results of reliability analysis from Study II.

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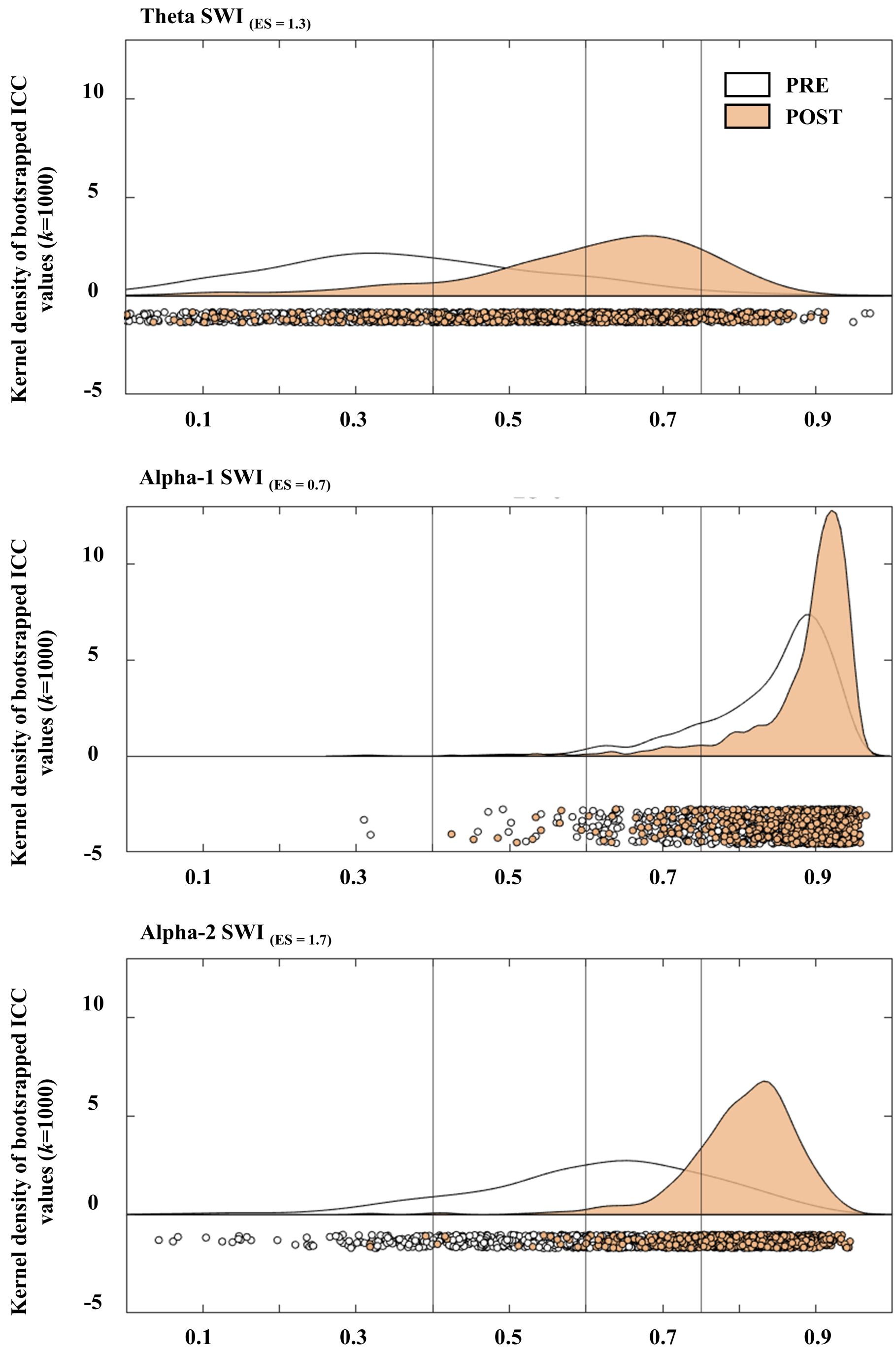

Figure 9. Main findings of relative reliability analysis from Study II. Raincloud plots displaying the distribution of ICC values for RSN outcomes before (PRE, white) and after (POST, orange) acute exercise for 10 minutes at 50 % vVO^2_{peak}. Distributions and estimated effect size (ES) rely on a comparison base on a resampling of *k*=1000 iterations using the *bootes* function (Di Plinio, 2022). Rainclouds display the kernel density distributions of the resampled ICC values, and dots indicate the *k*=1000 individual values extracted from bootstrapping. Small-world index (SWI) was computed for theta (4 to 8 Hz), alpha-1 (8 to 10.5 Hz), and alpha-2 (10.5 to 13 Hz) frequency bands. Horizontal lines indicate thresholds for fair (0.4, lower line), good (0.6, midline), and excellent (0.75, upper line) ICC values.

3.3 Study III: The mode of endurance exercise influences changes in EEG resting state graphs among high-level cross-country skiers (Büchel et al., 2023)

After extracting graph outcomes to quantify intensity-dependent changes of RSN organization in Study I and describing the reliability of the outcomes in a week-to-week analysis in II, Study III aimed to investigate the sensitivity of RSN organization toward manipulation of the prescribed exercise mode. Therefore, intensity-matched protocols on the treadmill were performed in two modes of different sensorimotor demands. In the first protocol, the prescribed exercise mode was running (RUN), while individuals were asked to XC ski (XC) on the treadmill for the second protocol. The study sample included fifteen highly trained XC skiers (age: 20.1 ± .6 years; weight: 74.4 ± 5.6 kg; size: 178.9 ± 5.5 cm; VO^2_{peak}: 65.3 ± 4.3 ml/min/kg) reporting a weekly endurance training load of ~ 20 hours.

The analysis of internal load revealed a significant main-effect of exercise intensity on the analyzed internal load parameters ($p<.001$). All outcomes demonstrated a gradual increase and reached maximal values for BS, B_{La}, and HR after the bout of exercise at 90% vVO^2_{peak} in both protocols ($p<.001$). An analysis of internal load toward exercise mode revealed comparable physiological responses comparing running and XC skiing since BS and B_{La} did neither show significant main- nor interaction effects concerning the exercise mode performed. Only HR was significantly higher for XC compared to RUN ($p=.005$). Figure 10 provides an overview of the physiological responses for both protocols.

For the analysis of exercise-induced modulations of RSN organization, both main-effects for exercise intensity and mode were observed. An effect of exercise intensity on RSN organization was observed in the theta band. Both SWI and CC decreased, while PL increased after the most intense bout of exercise at 90 % vVO^2_{peak} in both protocols ($p<.05$). Further, a mode-specific modulation in RSN organization was observed in the alpha-2 frequency. For both CC and SWI, increased values were observed following acute bouts of XC compared to RUN ($p<.05$). An overview of the modulations of the SWI in the theta and alpha-2 bands in response to the prescribed exercise protocols can be found in Figure 11.

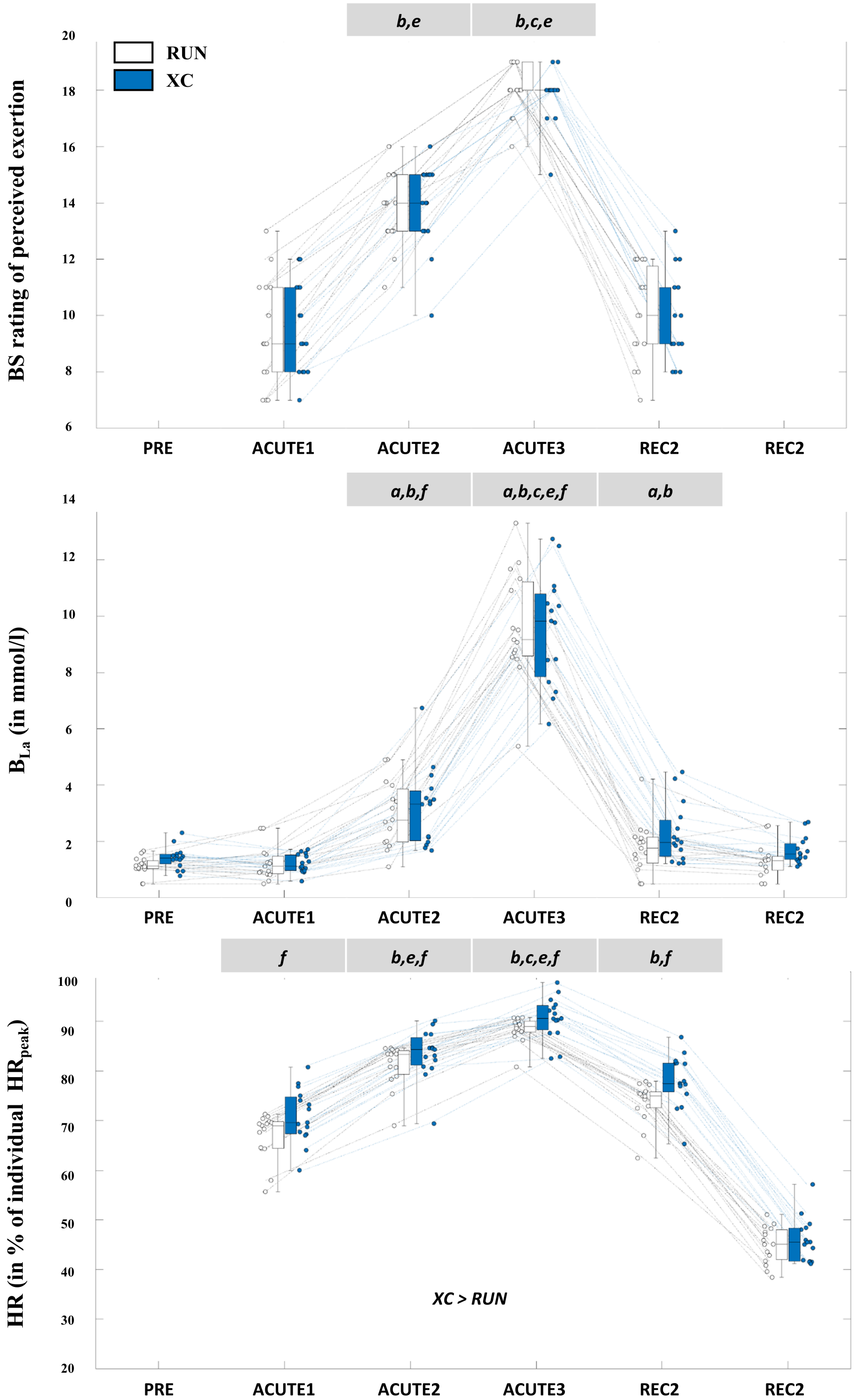

Figure 10. Main findings on physiological outcomes analyzed for Study III. ANOVA revealed modulatory effects of exercise intensity and mode on physiological outcome parameters. White bars indicate results from the running protocol (RUN), while blue bars display results from the roller-ski skiing protocol (XC). Main-effects of exercise intensity ($p<.05$) were observed for i) Borg scale rating of perceived exertion (BS, first panel), ii) blood lactate concentration (B_{La}, second panel), and iii) heart rate during exercise (HR, third panel). Significant differences between conditions ($p<.05$) revealed by post-hoc analysis are indicated in the grey boxes above each panel as follows: a = significantly higher than PRE, b = significantly higher than ACUTE1, c = significantly higher than ACUTE2, d = significantly higher than ACUTE3, e = significantly higher than REC1, f = significantly higher than REC2. Further, a main-effect of exercise mode was observed for HR ($p<.05$), demonstrating that HR was higher during XC compared to RUN.

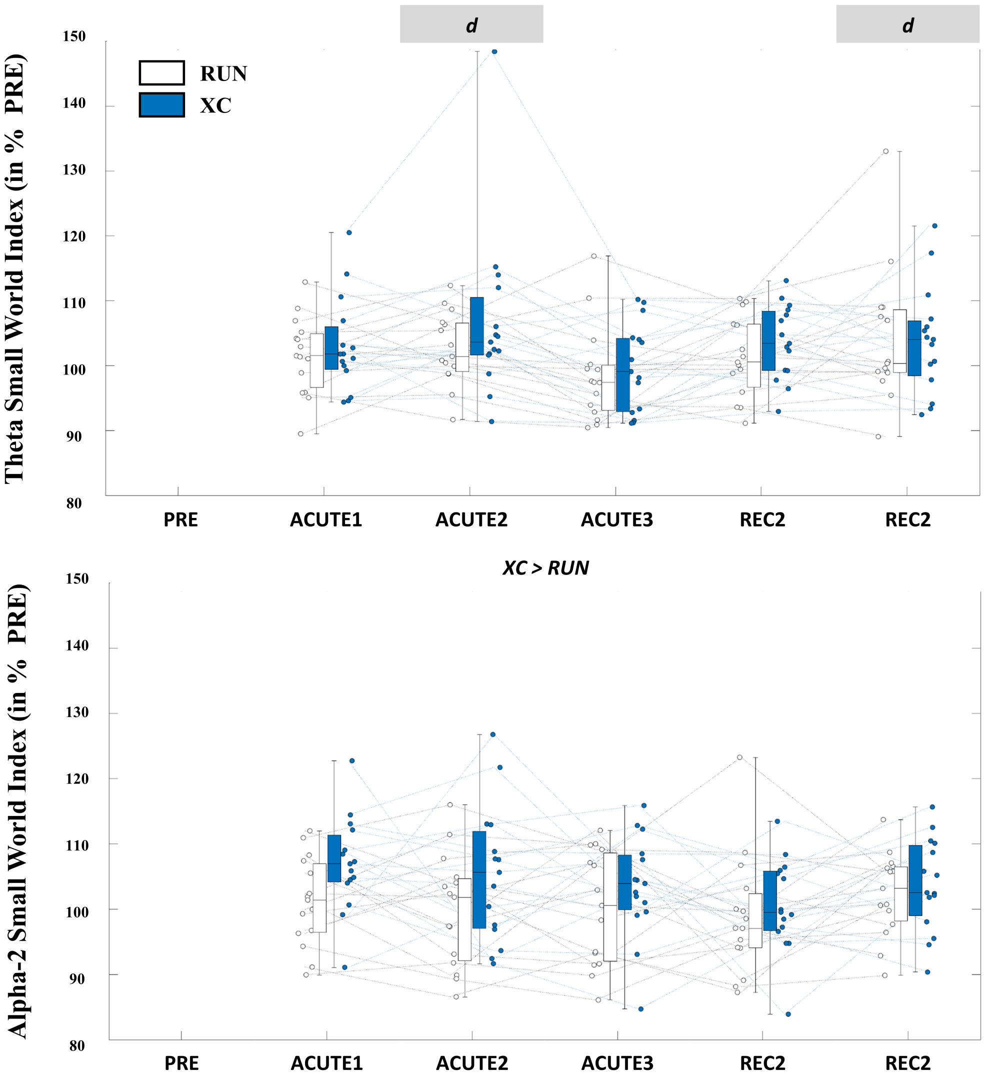

Figure 11. Main findings on neurophysiological outcomes analyzed for Study III. ANOVA revealed a modulatory effect of exercise intensity and mode on changes in RSN organization (in % PRE). White bars indicate results from the running protocol (RUN), while blue bars display results from the roller-ski skiing protocol (XC). A main-effect of exercise intensity (p<.05) was observed for small-world characteristics in the theta frequency band (4-8 Hz). Significant differences between conditions (p<.05) revealed by post-hoc analysis are indicated in the grey boxes above each panel as follows: d = significantly higher than ACUTE3. Further, a significant main-effect (p<.05) of exercise mode was observed on small-world characteristics in the alpha-2 band (10-13 Hz), demonstrating that SWI changes were higher during XC compared to RUN.

4 Discussion

In the final chapter, the findings of the three investigations which were conducted for the present thesis will be discussed. Initially, the main findings of each study will be summarized and interpreted briefly. Further, methodological considerations in the scope of the overall aim of the present thesis will be depicted. Therefore, specific strengths and limitations of the chosen approach toward the exploration of acute exercise-brain-interactions will be reflected. Finally, potential fields of research and practical applications arising from the findings of the present thesis will be elaborated. A more detailed discussion of the specific findings of each investigation can be found in the articles of the corresponding manuscripts.

4.1 Summary of the key findings

The present thesis aimed to explore the dose-response-relationship between acute exercise and brain function. To overcome issues of applicability and portability for future research in the field of exercise neuroscience, the EEG was utilized to reconstruct RSNs based on a portable method with high temporal resolution. Throughout the three conducted studies, the specific objectives were: i) to examine the effect of exercise intensity on EEG-derived RSN organization, ii) to quantify the week-to-week reliability of the extracted outcomes, and iii) to explore the moderating role of exercise mode on acute modulations of RSN outcomes.

In Study I, the analysis of RSN organization revealed systematic modulations of RSN organization as an acute response of the CNS to exercise of incremental intensity. After the most exhaustive bout of exercise, RSN organization in the theta frequency band changed and indicated reduced small-world characteristics. Previous investigations associated this pattern with reduced efficiency of attention-related brain networks (Vecchio et al., 2017). At the time-point of reduction in theta SWI, participants approached the limit of their individual performance capacity. The state of exhaustion through exercise was indicated by an average HR close to the individual maximum (> 90 %), severe subjective perceived exhaustion (BS value 19 out of 20), and B_{La} concentration values indicating a strong lactate accumulation (~ 8 mmol/l). The non-linear, intensity-dependent effect of exercise on CNS function observed in Study I is in line with existing findings on intensity-specific changes in RSNs from fMRI investigations (Bao et al., 2019; Schmitt et al., 2019). The reduction of efficiency of communication on the neurophysiological level could be a hallmark of reduced cognitive and sensorimotor performance after bouts of exercise with maximal intensity (McMorris et al., 2015). Therefore, the findings of Study I demonstrate that the reconstruction of RSNs serves as a feasible and portable neurophysiological approach to measure acute exercise-induced changes in brain function.

The aim of Study II was to assess the test-retest reliability of the RSN outcomes investigated in Study I. On account of that, individuals performed the same bout of low-intensity exercise twice within one week and the EEG resting state recordings before and after the acute bouts of exercise were analyzed for reliability. The analysis of relative reliability revealed a range of poor to excellent ICC scores for the extracted RSN. Notably, variations in reliability were observed with regard to i) the specified frequency band as well as ii) the time point of EEG recording. Concerning the frequency bands, the obtained ICC scores were moderate-to-good for outcomes in the theta band and good-to-excellent for outcomes in the alpha-1 and alpha-2 bands. In terms of absolute reliability, the analysis revealed good CoV values (< 5 %) in the theta and alpha-2 bands and moderate CoV values (< 10 %) in the alpha-1 band. The findings on frequency-specific reliability of EEG-based graph metrics follow previous investigations suggesting both methodological and functional reasons for the observation (Hardmeier et al., 2014; Kuntzelman & Miskovic, 2017). On the one hand, methodological aspects like the choice of epoch length and FC metric seem to affect frequency-specific reliabilities (Fraschini et al., 2016; Kuntzelman & Miskovic, 2017). Further, the functional roles of the frequency bands might affect reliability, since theta frequencies are associated with dynamic state-related functions such as attention (Cavanagh & Frank, 2014), while alpha oscillations are linked to inhibitory networks particularly active at rest (Klimesch, 2012). In addition, the absolute and relative reliability of RSN outcomes increased after a low-intensity bout of exercise compared to full rest before exercise. The increased reliability might be associated with the neuroregulatory effect of acute exercise and the release of exerkines which may contribute to a more systematic communication across brain networks (Basso & Suzuki, 2017). Accordingly, it can be assumed that EEG-derived RSNs serve as a reliable approach to quantify modulations in brain function, particularly after exercise.

However, frequency-specific week-to-week variations should be taken into account when interpreting acute and chronic RSN modulations.

After examining the feasibility and reliability of RSN analysis, Study III aimed to explore the modulatory effect of exercise mode on RSN organization. Therefore, acute, exercise-induced changes in RSN organization were examined with regard to two exercise variables: i) exercise intensity and ii) exercise mode. The comparison of RSN modulations in response to intensity-matched treadmill protocols of running and XC skiing revealed two key observations. Firstly, the findings of Study I were confirmed since both exercise modes induced significant deteriorations of efficiency – indexed by reduced segregation and higher integration -in the theta network after exhaustive exercise. Therefore, it might be assumed that exhaustive exercise induces detrimental effects on attention-related brain function (McMorris et al., 2015). Secondly, XC skiing had a significantly stronger modulatory effect on the small-world organization in the alpha-2 RSN compared to running. Since both protocols induced highly comparable physiological responses, these differences are likely to arise from mode-specific differences between running and XC skiing. In this regard, i) the involvement of the upper body, ii) the sports-specific technique and iii) the utilization of poles and skis (Pellegrini et al., 2018; Ø. Sandbakk & Holmberg, 2017) seem to be important differences comparing the locomotion characteristics of XC skiing and running. The EEG oscillations in the alpha-2 frequency are related to the active inhibition of task-irrelevant information in cortico-cortical neural circuits (Klimesch, 2012). During locomotion, modulations in the alpha-2 frequency have been observed in response to increasing demands on postural control (Sipp et al., 2013), upper body involvement (Kline et al., 2016), and inter-limb movement coordination (Weersink et al., 2021). Therefore it might be suggested that the different sensorimotor demands between the modes contributed to alterations in network efficiency in the alpha-2 frequency. Consequently, mode-specific aspects such as the sensorimotor demands seem to act as additional moderators of the acute interaction between exercise and brain function,

Taken together, the current thesis revealed promising insights into the dose-response-relationship between acute exercise and RSN organization. By the findings of the three included studies, intensity- (Study I) and mode-specific (Study III) characteristics of an exercise dose play an important role in the acute interaction between exercise and brain function. Further, Study II indicated that these modulations can be quantified reliably in repeated measures designs. Therefore, it might be assumed that the EEG-based RSN analysis is a feasible and reliable approach to quantify dose-specific modulations of brain function in response to exercise. The complex interaction between acute exercise and CNS function underlines the important role of the brain in exercise physiology.

4.2 Methodological considerations

The present thesis granted specific insights into acute exercise-induced changes in RSN organization. Throughout the process of planning, conducting, and analyzing the three included studies, several methodological decisions were made. In the upcoming section, these decisions will be critically reflected and the strengths and limitations of the thesis will be discussed concerning its major aim. To account for the interdisciplinary character of the conducted research, the methodological considerations will be reflected through i) a methodological perspective reflecting the usage of the EEG, ii) a neuroscientific perspective discussing the RSN approach, and iii) an exercise scientific perspective evaluating the designed exercise protocols.

4.2.1 Strengths and limitations of the EEG as a portable neurophysiological method

The present thesis aimed to quantify exercise-induced changes in brain function based on a portable neurophysiological approach utilizing the EEG. The findings of Studies I to III demonstrated that the reconstruction of RSN organization derived from EEG recordings provides specific insights into the dose-response-relationship between exercise and CNS function. The main findings revealed dose-specific transient modulations of brain function with regard to the two exercise variables intensity (Study I and III) and mode (Study III). These findings fall into the scope of recent fMRI-based investigations demonstrating dose-specific modulations of RSNs when comparing exercise doses of different intensities (Schmitt et al., 2019) or modes (Ueta et al., 2022). Therefore, the EEG might serve as a portable and fast applicable neurophysiological method to measure transient changes in RSN organization induced by exercise.

The usage of a saltwater-based EEG system reduced the time between exercise cessation and the start of the recording to ~ 3 to 6 minutes, while the methodological characteristics of the fMRI extend this time window to ~ 20 minutes (Rajab et al., 2014; Weng et al., 2016). A short preparation time can be beneficial because recovery processes start shortly after cessation of the exercise and may reverse the transient exercise-induced changes in brain function when the time between exercise and the start of the recording is too long (Herold et al., 2019). Additionally, the reduced preparation times of the EEG allowed for conducting repeated recordings throughout an intermittent bout of exercise. Therefore, the measurement frequency was increased and permitted a more detailed analysis of the time course of RSN modulations after exercise. In contrast, the most applied method to date – the fMRI - is restricted to single neurophysiological recordings before and after exercise (Rajab et al., 2014; Weng et al., 2016). Additionally, the increased degrees of freedom regarding portability make the EEG a suitable and highly applicable method for the systematic exploration of brain-exercise-interactions in lab and field conditions (Mehta & Parasuraman, 2013; Park et al., 2015). Despite the high portability, it is worth noting that all experiments included in the present study were conducted under controlled laboratory conditions to standardize the prescribed exercise doses. However, the chosen methodological approach also appears feasible for non-laboratory environments such as locker or treatment rooms in sporting facilities. Therefore, future studies can consider applying the elaborated RSN approach outside of the lab environment and making use of the portability of the EEG in real-world environments (M. Chang et al., 2022; Ladouce et al., 2019).

Despite its advantages in applicability, the limited spatial accuracy and the issue of volume conduction remain the major methodological downsides of the EEG (Mehta & Parasuraman, 2013). Therefore, investigations of EEG-derived RSNs are limited to the interpretation of the spatial characteristics of the reconstructed brain networks, especially in the sensor space. One approach to increase the spatial accuracy of the EEG is the analysis of source-reconstructed networks (C. Li et al., 2017). However, source-space reconstructed networks show lower reproducibility compared to the chosen channel-based approach and make the interpretation of RSN modulations in longitudinal designs more difficult (Fraschini et al., 2021). Further, even source-reconstructed EEG networks remain affected by volume conduction and do not solve the inverse source problem completely (Palva et al., 2018). To account for the issues of limited spatial resolution and volume conduction of EEG-derived brain graphs, the present thesis explored changes in

RSN organization i) within subjects and ii) on the base of global graph metrics. On the one hand, global graph metrics do not make assumptions about specific brain regions and are less affected by lacking spatial information on the sources of the observed electrophysiological phenomena (Miljevic et al., 2022). On the other hand, the mixed sources in the electrode subspace are suggested to remain stable across repeated measures of the same individual and therefore reduce the issues arising from the inverted-source problem and volume conduction in within-subject investigations (Lai et al., 2018). Nevertheless, the inherent limitations for the spatial organization of RSNs should be considered when applying the EEG.

While the spatial inaccuracy is a clear limitation of the chosen approach, the high temporal resolution of the EEG allows for a more particular analysis of neural activity compared to metabolic methods due to the spectral decomposition of the recorded signal (Mehta & Parasuraman, 2013). In the three included studies, frequency-specific effects of different exercise doses on RSN organization were observed in the theta and alpha-2 frequency bands. While theta oscillations are associated with processes of adaptive control originating in the frontal cortex (Cavanagh & Frank, 2014), alpha-2 oscillations are related to inhibitory processes which are generated through communication between cortical and subcortical brain structures (Klimesch, 2012). Accordingly, the temporal resolution of the EEG may counteract the limited spatial accuracy by adding contextual information which supports the functional interpretation of the observed modulations of RSNs.

Another important issue of non-invasive neurophysiological methods like the EEG is the impact of systemic physiological responses like sweating or altered electro dermal activity on the recorded signal (Stone et al., 2018). Particularly after acute bouts of exercise, systemic physiological reactions turn into additional non-cortical sources contributing to the recorded EEG signal. For instance, sweating affects the EEG through slow potential drifts caused by alterations of electro dermal activity at the scalp (Stone et al., 2018). Although the applied filtering techniques and the removal of electrical bridges reduced the impact of sweating on the recorded signals, future studies need to keep in mind that systemic physiological processes can bias neurophysiological recordings in post-exercise EEG assessments.

Taken together, the methodological advantages of the EEG concerning its high temporal resolution and high applicability granted specific insights into the dose-response-relationship between exercise and brain function. When considering aspects such as the limited spatial resolution for the interpretation of the recorded data, the EEG serves as a valid and reliable tool to investigate modulations of brain function in sports and exercise.

4.2.2 Strengths and limitations of the RSN approach to investigate dose-response-relationships between exercise and brain function

The findings of the included studies demonstrate that exercise-induced modulations of CNS function seem to be transient and can be therefore measured at rest after exercise. Consequently, the assessment of RSNs seems to be a promising approach to explore dose-response-relationships between exercise and CNS function. Despite the emerging impact of mobile brain imaging studies utilizing the fNIRS and EEG (Kenville et al., 2017; Visser et al., 2022), the RSN approach circumvents the issues arising from movement-artifact (Gorjan et al., 2022) and is less domain-specific when compared to task-positive approaches (Hausman et al., 2020). Further, EEG resting state recordings traditionally analyzed the transient modulations of brain function through exercise based on changes in activity in predefined brain areas, e.g. the frontal or parietal cortex (Gramkow et al., 2020). The network approach chosen for the present thesis allowed for a more holistic quantification of brain function by considering the key strategies of the brain in terms of functional integration and segregation (Friston, 2002). So, the assessment of RSNs is suggested to be a feasible and efficient approach to explore exercise-induced modulations of brain function.

Besides demonstrating the feasibility of the RSN approach in Study I and III, Study II quantified the week-to-week reliability of the EEG-derived RSN measures. The findings revealed moderate to excellent reliability scores for the RSN outcomes, with considerable differences associated with the different frequency bands and the time point of measurement. While RSN outcomes in the alpha bands yielded excellent reliability ICC scores, outcomes in the theta band only revealed moderate to good relative reliability. Further, reliability scores were significantly improved for RSN outcomes assessed after an acute bout of low-intensity exercise. Therefore, it might be suggested that the EEG-derived assessment of RSN organization is an overall reliable approach to investigate modulations of brain function after exercise. The information on the reliability across frequencies and time points is crucial for an adequate interpretation of RSN modulations since it provides an estimate of the potential, non-experimental variability of the examined outcomes in repeated measures designs.

As a key finding, Study II revealed that the week-to-week reliability of RSN outcomes seems to be frequency-dependent. From a neurophysiological point of view, the differences in the reliability of RSN organization between the theta and alpha frequencies might be partly related to the associations of the different frequency bands with distinct brain functions. For instance, alpha oscillations are associated with large-scale thalamocortical and cortico-cortical inhibitory networks which are involved in the inhibition and gating of task-relevant information (Klimesch, 2012). Since these neural connections are particularly active at rest, it seems reasonable that global RSN outcomes in the alpha-bands demonstrate high reliabilities in task-off situations (Ding et al., 2022). In contrast, theta oscillations are associated with task-related activity in the frontal lobe and contribute to processes of adaptive control but are also involved in drowsiness (Cavanagh & Frank, 2014; Snipes et al., 2022). Therefore, the temporary and state-dependent processes associated with the theta frequency may result in more substantial day-to-day variations of global RSN outcomes. Interestingly, distinct reliabilities of RSNs concerning the functional role of the network have also been reported for RSNs derived from fMRI (Tozzi et al., 2020). Accordingly, the frequency-specific reliabilities may result from the functional roles of the underlying neural ensembles and are important to consider when interpreting findings in RSN investigations.

Further, the limited reliability in the theta frequency is not solely a methodological limitation, but could also be considered an opportunity for insights into a dynamic physiological system. Since functional brain networks rely on both the functional and structural connections between neurons, the acute organization of an RSN is always a product of the more stable, chronic adaptations and the more varying acute modulations of CNS function (Honey et al., 2010). The acute proportions of an RSN seem to be affected by temporary changes like mental state and can therefore result in variations of RSN organization within short periods (Geerligs et al., 2015; Hallett et al., 2020). Especially for the theta network, brain oscillations are associated with the two contrary mental states of attention and drowsiness (Snipes et al., 2022). Therefore, more fluctuating outcomes of brain function such as the theta RSN may gran insights into a dynamic neurophysiological system in the context of attention and drowsiness. Adding these CNS-related outcomes to established subjective and objective training monitoring variables could help to better understand the variable interplay between the brain and human performance over time.

Moreover, Study II revealed that the reliability of RSN outcomes increased after exercise. In particular, the two RSNs modulated by exercise intensity (theta) and mode (alpha-2) were more reliable when assessed after an acute bout of low-intensity exercise. It might be suggested that the exercise-induced release of exerkines (Vints et al., 2022) and acute changes in cerebral perfusion (J. C. Smith et al., 2010) contribute to a more systematic communication between neuronal resources after a bout of low-intensity exercise. The good reliability of RSN measures after exercise is a promising indication for the integration of RSN outcomes into repeated measures scenarios such as training monitoring (Perrey, 2022; Seidel-Marzi & Ragert, 2020).

However, despite the reliable and valid insights, two important limitations of the RSN approach should be considered. From a methodological perspective, there is no current gold standard for the reconstruction RSNs based on the recorded EEG raw data (Miljevic et al., 2022). Therefore the decisions made throughout the processing of the data in the present thesis are based on methodological recommendations from previous studies (Fraschini et al., 2016; Lai et al., 2018; Vinck et al., 2011). Nevertheless, it was reported that methodological decisions such as the chosen FC metric and epoch lengths can affect the reconstruction of RSNs (Fraschini et al., 2021; Hardmeier et al., 2014; Kuntzelman & Miskovic, 2017). To address this issue, several authors have suggested implementing multiple FC metrics and epoch lengths to answer a given research question (Kuntzelman & Miskovic, 2017; Miljevic et al., 2022). Due to the applied character of the present thesis, only one plausible methodological approach was prioritized to gain an explorative insight into RSN dynamics. Hence, it cannot be ruled out that different methodological choices on the way from the raw data to the final RSN outcomes could have led to deviating modulations and reliabilities.

Moreover, the reduced domain-specificity in RSN investigations is suggested to reduce the impact of task difficulty and expertise on the extracted CNS outcomes (Hausman et al., 2020). However, since the recording of RSNs rules out the concomitant recording of behavioral data, the functional consequences of the observed transient modulations in the theta and alpha-2 frequency band on neural processes underlying sports performance such as sensorimotor control and cognition remain hypothetic. While some RSN investigations associated efficiency in the alpha network with the subsequently assessed non-verbal intelligence in healthy individuals (Zakharov et al., 2020), other studies associated disruptive organizations of RSNs with cognition and cognitive disorder on the group level comparing healthy and disordered individuals (Miraglia et al., 2022). Since the present studies did not quantify additional behavioral data before or after the RSN recordings, the observed transient modulations of RSN organization cannot be linked to behavioral correlates directly. Therefore, future studies should aim to quantify such changes in behavior after the recording of EEG resting states to better understand the behavioral consequences of transient modulations of RSN organization.

Taken together, the analysis of RSNs seems to be a feasible and reliable approach to examine dose-response relationships between exercise and brain function. The limited reliability of distinct RSN outcomes should be considered since both functional and methodological are likely to limit the reproducibility of brain graphs. To further increase the value of RSN assessments for exercise physiology, future studies should assess complementary contextual and behavioral outcomes to understand the functional consequence of transient modulations of RSNs.

4.2.3 Strengths and limitations of the prescribed exercise protocols

The repeated analysis of RSN organization throughout incremental and individualized protocols aimed to explore the dose-response relationship between acute exercise and brain function. The findings of Studies I and III revealed that an acute bout of exhaustive exercise intensity seems to induce a short-term deterioration of network efficiency in the theta network. Further, the findings of Study III yielded modulations of network efficiency in inhibitory brain networks of the alpha-2 frequency concerning the performed mode of exercise. Therefore, the prescribed exercise protocols allowed for the exposure of the individuals to specified doses of exercise which modulated cortical RSNs differentially. For both the intensity- and mode-specific observations, specific strengths and limitations need to be taken into account.

In Studies I and III, exercise intensity was individualized based on the assessment of VO^2_{peak} of each participant before the actual experimental trial. This measure allowed for a standardized and individualized prescription of exercise intensity (Herold et al., 2019). The individualization of the exercise dose based on internal load is particularly important since an assignment of intensity based on markers of internal load can lead to highly variable exercise responses even within homogeneous groups of individuals. Apart from the pre-assessment of aerobic capacity, multiple physiological outcomes were monitored throughout the protocols using HR, B_{La}, and BS. These outcomes provided insights into the physiological systems associated with endurance performance (Halson, 2014). In sum, the pre-assessment of aerobic fitness and the monitoring of internal load throughout all studies allowed for the objective verification of two important assumptions on the prescribed doses of exercise. On the one hand, the gradual increase in internal load throughout the protocol was verified objectively for Study I and III. On the other hand, the agreement of exercise intensity between the two modes of running and XC skiing was proven for Study III. Therefore, the additional assessment of physiological variables before and during the experiment allowed for an objective specification of the induced doses of exercise.

One main observation of this thesis was the transient disturbance of network efficiency after exhaustive exercise. Notably, this pattern was observed independently from i) the performed endurance mode and ii) the fitness level of the examined sample. The observation of similar RSN modulations after both exhaustive running and XC skiing exercises seems reasonable because both modes require a highly developed cardiovascular system (Ø. Sandbakk et al., 2021). Since the quantified internal load indicated a comparable state of exhaustion at the time point of deterioration of RSN efficiency for both modes, it might be assumed that this modulation is induced by the energetic demands of an acute bout of exercise. Secondly, the deterioration of RSN efficiency has been observed independently in both investigated samples, the recreationally active individuals from Study I as well as the highly trained athletes from Study III. Therefore, the observed effect seems to be independent of the individual fitness level, although aerobic fitness has been raised as a potential moderator of the acute response of the CNS to exercise (Huang et al., 2014; Salzman et al., 2022). Since both groups revealed maximal responses of HR (90.4 and 88.8 % HR_{peak}), B_{La} (7.9 and 9.6

mmol/l), and BS (18.9 and. 18.0) in Study I and III, respectively, it could be suggested that the magnitude of energetic stress experienced by the individual is one key stimulus for transient modulations of brain function. Based on the observation of deteriorated network efficiency after exhaustive exercise in all sub-experiments of this thesis, the prescribed protocols support assumptions that exercise intensity acts as a key moderator in the interplay between exercise and brain function (Herold et al., 2019; Hortobágyi et al., 2022).

However, it is also important to discuss the limitations of the intensity-related findings of this thesis. The analysis of RSN organization throughout the exercise protocol did not reflect the proposed facilitative part of the intensity-dependent relationship between acute exercise and brain function (Y. Chang et al., 2012; McMorris & Hale, 2012). Based on neurophysiological findings from fMRI investigations (Rajab et al., 2014; Schmitt et al., 2019; Weng et al., 2016), facilitation of RSN organization would have been expected after submaximal exercise intensities, but neither Study I nor Study III revealed relatable patterns. A possible reason might be the actual duration and intensity of the prescribed doses of exercise. In Studies I and III of this thesis, average HR reached 80.1 ± 5.2 % and 81.1 ± 4.3% of HR_{peak} during the moderate running intervals, respectively. In contrast, the prescribed intensity in the cited fMRI studies was lower and average HR ranged from ~ 61.5 % (Schmitt et al., 2019) to ~ 70 % (Rajab et al., 2014) of predicted HR_{peak}. Therefore, the higher average intensity in the present investigation may be one reason why RSN efficiency did not improve. In addition, the present study investigated changes in RSN organization through an intermittent protocol to allow for repeated EEG resting state recordings. Consequently, the summated exercise duration of > 35 minutes was split into four single bouts of ~ 8-10 minutes with intermittent breaks of ~ 8 minutes. In contrast, previous RSN studies performed continuous exercise bouts of 25 (Rajab et al., 2014) to 35 minutes (Schmitt et al., 2019). Since a minimum exercise duration seems necessary to induce facilitating effects on brain function (Y. Chang et al., 2012; Dinoff et al., 2017), the single bouts of exercise could have been too short for facilitative modulations of brain function. As a result, the prescribed training dose as the product of duration and intensity (Herold et al., 2019) might have been too short and too high to induce facilitations of brain function. Moreover, the observed inter-individual differences in physiological responses at submaximal stages are likely to contribute to the lack of facilitating effects on RSN organization. Following the exercise interval at 70 % vVO^2_{peak}, the average B_{La} was 2.8 ± 1.3 and 3.2 ± 1.3 mmol/l in Study I and III, respectively. Therefore, the average B_{La} falls into the range of various suggested thresholds of anaerobic metabolism between 2.5 and 4.0 mmol/l (Faude et al., 2009). To reduce the heterogeneity across individuals at submaximal intensities and streamline internal load, future studies should consider prescribing exercise submaximal intensities under consideration of metabolic thresholds (Herold et al., 2019).

Next to the intensity-specific effects on brain function, Study III also revealed that the prescribed mode of exercise influences the transient modulations of brain function following exercise. In particular, the findings of Study III indicated that XC skiing exercise-induced significantly higher modulations of RSN efficiency in the alpha-2 band compared to running exercise. Since, exercise mode has been barely considered as a moderator of the acute modulatory effect of exercise on brain function (Brümmer, Schneider, Abel, et al., 2011; Ueta et al., 2022), Study III is one of the first investigations to indicate mode-specific modulations of brain function after an acute bout of exercise.

To explore the modulatory effect of exercise modes on brain function systematically, the entity of quantitative and qualitative characteristics of the induced doses of exercise were considered. In the context of exercise neuroscience research, Voelcker-Rehage & Niemann (2013) suggested differentiating between energetic and sensorimotor modes. While energetic modes like running are suggested to modulate brain function through peripheral processes like the release of exerkines, sensorimotor modes like balance exercise were stated to affect brain function through the direct recruitment of task-relevant neural resources (Voelcker-Rehage & Niemann, 2013). Therefore, Study III examined two exercise modes with comparable energetic but differential sensorimotor profiles to isolate the modulations of brain function arising from sensorimotor demands from those arising from the energetic demands of exercise. The matched energetic demands of XC skiing and running were verified objectively through the monitoring of internal load. Accordingly, the objective verification of similar energetic profiles of the two modes ruled out that different energetic demands influence the mode-specific modulations of brain function. Furthermore, the matched energetic demands facilitated the interpretation of the mode-specific transient modulations of brain function concerning the sensorimotor characteristics of the compared exercise modes.

While the energetic demands of a mode of exercise can be characterized through objective measures like HR and B_{La}, the differentiation between sensorimotor demands of the two compared modes rather relied on descriptive, qualitative aspects. Sensorimotor demands like the utilization of sports-specific techniques or the involvement of both upper and lower body muscles in locomotion differentiate XC skiing from running (Pellegrini et al., 2014; Ø. Sandbakk & Holmberg, 2017), but are complex to be characterized objectively. Although Pesce (2012) pointed out that qualitative aspects are highly important for the acute effect of exercise on brain function, a framework to systematically compare sensorimotor demands across different modes of exercise is still lacking. A variable with the potential to summarize the sensorimotor demands of a given mode of exercise is exercise complexity. It has been stated as the key variable determining the exercise-brain interactions for sensorimotor exercise since it is related to the demands on information processing and the task-related recruitment of neural resources (Carey et al., 2005; Netz, 2019). Nevertheless, a clear definition of complexity as a characteristic modulating the prescribed dose of exercise is missing. Therefore, the observed findings need to be treated as a specific observation for the comparison of running and XC skiing. Since the potential stimulating parameter of the observed effect, the exercise complexity, remains qualitative and descriptive, transfers to other exercise modes need to be done with caution.

As another more generic limitation, it is worth mentioning that the present thesis only included male and active individuals. Due to the explorative character of this thesis, a maximally homogeneous sample was examined and inter-individual factors such as sex, age, fitness level, or expertise were standardized. While neurophysiological techniques provide initial insights into fitness-specific modulations of brain function (Ludyga et al., 2016), expertise-related effects on brain function have been widely discussed in the context of the neural efficiency hypothesis (L. Li & Smith, 2021). Nevertheless, no study to date has considered the effect of age and sex on transient modulations of brain function after exercise, although sex- or age-related aspects like the menstrual cycle in females (Haraguchi et al., 2021) or cognitive decline across the lifespan (Vecchio et al., 2022) likely modulate the responsiveness of the CNS to exercise. Therefore, it should be considered that the homogeneity of the investigated sample regarding sex, age, and fitness level may have resulted in sample-specific findings. To overcome this issue, future studies should aim to investigate samples with specified subgroups to better understand the role of inter-individual factors in the acute interaction between exercise and brain function.

Overall, the prescription of exercise doses through incremental treadmill protocols in two different endurance modes granted novel insights into the interplay between acute exercise and brain function. The findings of this thesis revealed dose-specific modulations in RSNs modulated by the energetic and sensorimotor demands of the exercise. The individualization of exercise intensities and the monitoring of internal load allowed to induce incremental doses of exercise in the individuals. The comparison of two different exercise modes with similar energetic demands revealed initial insights into the role of sensorimotor demands and exercise complexity on transient changes in brain function. Since the role of exercise mode in the dose-response relationship between exercise and brain function remains unclear, systematic research is required to specify the influences of energetic and sensorimotor exercise characteristics on brain function.

4.3 Contributions of the RSN approach to integrate the brain in exercise physiology

In the present thesis, a portable and quick applicable approach was utilized to examine transient exercise-induced changes in brain function. The three included studies demonstrated that the reconstruction of cortical RSNs seems to be feasible (Study I), reliable (Study II) and dose-sensitive to quantify interactions between acute exercise and brain function (Study III). Hence, the RSN approach allows for an assessment of the functional organization of the brain in prescribed exercise scenarios and could grant insights into the acute responses and chronic adaptations of the brain to exercise.

Although the CNS is the physiological system responsible for the processes of sensorimotor control and cognition, it is barely considered in exercise physiology research (Perrey, 2022). The major barriers to the integration of neurophysiological methods are the limited portability as well as the susceptibility of the applied methods to movement artifacts limiting the reliability of the data (Perrey & Besson, 2018). The findings of this thesis demonstrate that the reconstruction of RSNs based on EEG might be a feasible and reliable approach to quantify transient modulations of brain function induced by specified doses of exercise. Therefore, the RSN approach promises novel opportunities to examine the dose-response relationship between acute exercise and brain function due to a portable neurophysiological method.

Since the functional integration of information across the cortex forms the base for complex sensorimotor and cognitive processes, it is vital for skilled sports performance (Yarrow et al., 2009). The findings of Study I-III indicated that specific doses of exercise transiently modulate the functional integration of information within the cortex. Therefore, the reconstruction of RSNs may allow for the integration of CNS outcomes into applied exercise physiology research with a potential impact on sports performance (Perrey, 2022). In contrast to the fMRI, the EEG is a portable technology that can also be applied in research outside of the laboratory environment (Ladouce et al., 2019). Further, the RSN approach also minimizes issues related to artifacts originating from dynamic and intense movement (Gorjan et al., 2022) since brain function is measured during breaks or after exercise cessation. Because of these increased degrees of freedom, research becomes less restricted to ergometer-based exercise and brain function can be monitored after exposure to prescribed doses of exercise in the real world. So, the qualitative aspects of exercise such as complexity which have been shown to modulate brain function (Study III) can be more easily considered for the dose-response relationship between acute exercise and brain function (Pesce, 2012). For instance, dynamic and complex exercise modes such as dancing (Zilidou et al., 2018) or open-skill sports like badminton (Gu et al., 2019) can be performed in stimulating real-world environments, while transient modulations on the CNS are assessed under standardized conditions after exercise. Since research on the behavioral level already suggested mode-specific improvements in cognitive function (Gu et al., 2019), the reconstruction of RSNs after acute or chronic interventions provides valuable insights into the neurophysiological mechanisms underlying improved behavior.

Since the relationship between exercise and brain function is highly dose-specific, embedding CNS measures in training monitoring also requires more systematic documentation of the training process. Study III demonstrated that the energetic and sensorimotor characteristics of an exercise dose may affect the transient modulations of RSN organization differentially. Therefore, it seems mandatory to collect detailed information on the induced exercise dose, which includes energetic characteristics such as intensity and duration, but also sensorimotor characteristics such as exercise complexity. Since RSNs can also be affected by acute changes in psychophysiological state(Geerligs et al., 2015), subjective outcomes like well-being or sleep quality should also be considered as potential intra-individual moderators in the relationship between exercise and brain function (Saw et al., 2016). Therefore, the inclusion of CNS markers into training monitoring is a promising approach to better understand variations and adaptations of human performance. Nevertheless, the complexity of the CNS requires holistic and extended documentation of data with a potential impact on the underlying neural processes.

Despite the promising opportunities for embedding the RSN approach into exercise physiology, it is important to highlight the need for further methodological developments regarding RSN reconstruction. Future studies should specifically aim to optimize and standardize the reconstruction of RSNs to reduce the methodological bias on the extracted outcomes (Miljevic et al., 2022). Further, it is worth noting that the presented approach is tailored toward the portable quantification of CNS function in applied exercise-related settings. On the one hand, the assessment of brain activity during activity remains highly important to understand the active contributions of the brain to adaptive behavior related to movement and sports activity. Further, the invasive extraction of blood markers like BDNF or the structural and spatial analysis of neural adaptations through MRI and fMRI remains imperative to improve our understanding of exercise as a “pill” to promote and recover health in clinical research. Therefore, the interdisciplinary field of exercise neuroscience requires the continuation of multidirectional research for a deeper understanding of the benefits of exercise toward brain function.

4.4 Practical applications & future directions

Since the CNS is the major instance for sensorimotor control and cognition, the opportunity to modulate brain function through exercise raises great interest in exercise neuroscience research (Basso & Suzuki, 2017; El-Sayes et al., 2019; Netz, 2019). The methodological features of the presented RSN approach move the limitations for the assessment of neurophysiological data in the field of exercise beyond the laboratory setting (Park et al., 2015). Thus, the function of the brain to process information can be assessed in more variable and ecologically valid exercise scenarios (M. Chang et al., 2022). Therefore, the proposed neurophysiological approach opens new possibilities for the investigation of acute and chronic adaptations of the brain to exercise.

Study III indicated that mode-specific sensorimotor demands induce specific modulations of RSN organization. While the energetic demands of exercise are the main variables to be manipulated to control the training process, the sensorimotor and cognitive complexity of exercise is barely considered in exercise physiology (Perrey, 2022). Therefore, the assessment of brain measures allows for the implementation of the physiological system responsive to these characteristics of exercise into training monitoring. Particularly in sports with mixed energetic and sensorimotor performance profiles like soccer or handball, the athletes are not only required to move but also to adapt behavior continuously due to ever-changing environments (Sheppard & Young, 2006). Thus, the need to process complex information over time may display an additional source of stress next to the pure energetic demands caused by movement. Processes such as mental fatigue are decisive for human performance but can be barely derived t established exercise physiology variables like HR or B_{La} (Van Cutsem et al., 2017). In consequence, approaches such as the reconstruction of RSN allow quantifying acute and transient modulations of CNS function through exercise and take the complex sensorimotor demands of given sporting activities into account. Accordingly, the interplay between exercise doses and human performance might be better understood when considering the physiological responses to exercise more holistically.

Besides the examination of the acute dose-response relationship between exercise and brain function, also the long-term adaptation of the brain to exercise is of special interest. Assuming that the transient modulations of the brain to specified doses of exercise may change over time as a function of chronic neuroplasticity (El-Sayes et al., 2019), modulations of RSN organization may resemble the chronic adaptations of brain structure and function (Honey et al., 2010). Therefore, the longitudinal assessment of RSNs may allow for the identification of desired training effects in the CNS like improved neural efficiency (L. Li & Smith, 2021), but also undesired maladaptation such as overtraining or chronic underperformance (Talsnes et al., 2023). Since overtraining is nowadays accepted as a complex phenomenon with neurophysiological contributions (Armstrong et al., 2022), objective data derived from the CNS can optimize the assessment and prevention strategies for long-term maladaptation. For instance, the blunted release of neurotransmitters in the overtraining state (Cadegiani & Kater, 2017) could be identified non-invasively through altered RSN modulations in response to exercise. Therefore, the reconstruction of RSNs in longitudinal approaches before and/ or after exercise could provide complementary information to anticipate training adaptations and desired performance development.

Next to the importance of the interplay between exercise and CNS function for sports performance, it also plays an essential role in the prevention and recovery of cognitive and sensorimotor function (Di Liegro et al., 2019). Especially in groups like children (Möhring et al., 2022), the elderly (Langhammer et al., 2018), or disordered populations(Bray et al., 2021), the exposure of the individual to tailored doses of exercise is an efficient interventional approach to increase or recover the functional capacity of the brain (Voelcker-Rehage & Niemann, 2013). Interestingly, both the theta and alpha-2 RSNs which were modulated by acute exercise in the present thesis were previously associated with cognitive dysfunctions in cross-sectional investigations. networks demonstrated deteriorated organization in individuals suffering from Alzheimer´s disease, depression, or schizophrenia when compared to young healthy controls (Sun et al., 2019; B. Tan et al., 2019; Vecchio et al., 2022). Therefore, the transient modulation of these RSNs due to tailored doses of exercise may stimulate the neurophysiological processes associated with the functional abnormality in the examined groups. The high applicability of the RSN approach increases the degrees of freedom in exercise prescription and permits a variable individualization of complexity, intensity, and duration to tailor doses of exercise. Over time, the repetition of these individualized stimuli may initiate the chronic adaptation of deteriorated brain functions and help to improve and recover brain function (El-Sayes et al., 2019). Taking this into account, the RSN approach could also provide important insights into acute responses and chronic adaptations to exercise in non-athletic populations as an objective and generic assessment of CNS function.

Overall, the increased portability of neurophysiological methods like the EEG increases opportunities in exercise neuroscience research to explore the dose-specific associations between exercise and brain function. The proposed scenarios of the application of RSN in exercise neuroscience indicate a wide range of potential research objectives. One pressing need is to further explore the effect of exercise dosing variables like intensity, complexity, duration, and frequency on the acute and chronic modulations of brain function. Further, inter-individual aspects such as fitness level, sex, age, or disease should be investigated as potential moderators of this interaction. Consequently, the integration of the brain into exercise physiology may allow for a more efficient prescription of exercise to improve, recover and prevent body function.

5 Conclusion

The present thesis aimed to explore the impact of acute bouts of exercise on the functional integration and segregation of cortical resting state brain networks. Compared to previous investigations using stationary methods like the fMRI, the EEG was applied as a portable technique allowing for the reconstruction of RSN. Following individualized and incremental bouts of exercise on the treadmill, dose-specific modulations of RSN organization were observed. The manipulation of exercise dose through intensity induced detrimental effects on the efficiency of attention-related RSNs after maximal intensities. Moreover, the manipulation of exercise mode to specify sensorimotor demands of the exercise dose resulted in increased efficiency in RSNs related to sensorimotor control. Additionally, the reliability of the extracted RSN outcomes has been quantified and was particularly good when EEG resting states were recorded after acute bouts of exercise. On account of that, the EEG may serve as a portable and non-invasive neurophysiological method to investigate the interaction between acute exercise and brain function.

The processing of information in the CNS for sensorimotor control and cognition is a central component of sports performance. The reconstruction of RSNs based on EEG seems to display an applicable way to include CNS outcomes in exercise physiology research. While the present thesis provided initial insights into dose-specific modulations of brain function, further investigations are required to understand the complex dose-response relationship between exercise and brain function. In this regard, the modulatory effects of energetic exercise variables like intensity and sensorimotor variables like complexity require a more systematic investigation. Further, individual aspects like age, fitness/ expertise, and sex should be considered as potential moderators of this interaction. Based on the longitudinal assessment of RSNs throughout the training process, the brain´s contributions to exercise physiology can be investigated to support the long-term development of body function in different groups of individuals like athletes or patients.

Scientific Dissemination

Peer-reviewed publications

- **Büchel D**, Jakobsmeyer R, Döring M, Adams M, Rückert U, Baumeister J (2019). Effect of playing position and time on-court on activity profiles in german elite team handball. *International Journal of Performance Analysis in Sports*. 19 (5): 832-844. doi.org/10.1080/24748668.2019.1663071.
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- **Büchel D***, Lehmann T, Ullrich S, Cockcroft J, Louw Q, Baumeister J (2021). Stance leg and surface stability modulate cortical activity during human single leg stance. *Experimental Brain Research*. 239: 1193–1202. doi.org/10.1007/s00221-021-06035-6.
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- **Büchel D**, Torvik PØ, Lehmann T, Sandbakk Ø & Baumeister J (2023). The mode of endurance exercise influences changes in EEG resting state graphs among high-level cross-country skiers. *Medicine & Science in Sports & Exercise*. Published ahead of publication (January 6). doi.org/10.1249/MSS.0000000000003122

* shared first authorship of the first two authors listed in the publication

Book chapters

- Gokeler A., **Büchel D**. (2020). Pre-seasonal Assessment and Performance Diagnostics: Orthopaedic and Functional Aspects. In: Krutsch W, Mayr HO, Musahl V, Della Villa F, Tscholl PM, Jones H (Eds). Injury and Health Risk Management in Sports. Springer Verlag: Berlin-Heidelberg. doi.org/10.1007/978-3-662-60752-7_12

Proffered presentations

- **Büchel D**, Jakobsmeyer R, Döring M, Adams M, Rückert U & Baumeister J (2018). On-court activity profiles in german Bundesliga elite team handball. Oral presentation at the 2nd Scandinavian Congress in Handball Medicine and Science in Copenhagen, Denmark.

- **Büchel D**, Chang M, Lehmann T & Baumeister J (2020). Playing the brain - Neurophysiological evidence for cortical processing during table tennis. Oral presentation at the 25th European Congress for Sports Sciences (Virtual).
- **Büchel D**, Allen C, Lehmann T, Sandbakk Ø & baumeister J (2022). Changes in EEG Microstate Patterns Following exhaustive Treadmill Exercise Employing Reduced Channel Resolution. Oral presentation at the Congress of the American College of Sports Medicine 2022 in San Diego, United States.

Poster presentations

- **Büchel D**, Koers T, Grundmann R, Jakobsmeyer R & Baumeister J (2016). Positionsspezifischer Zusammenhang von Ausdauerleistungsfähigkeit und Laufleistung im Profifußball. Presentation at the 47th Congress of German Sports Medicine in Frankfurt (Main), Germany.
- **Büchel D**, Lehmann T, Cockcroft J, Louw Q & Baumeister J (2018). Effect of cognitive dual task on cortical activation during static postural control. Poster at the 3rd International Mobile Brain/Body Imaging Conference in Berlin, Germany.
- **Büchel D**, Döring M & Baumeister J (2018). Effect of match and travel on perception of wellness in world class handball players. Poster at the 2nd Scandinavian Conference in Handball Medicine and Science in Copenhagen, Denmark.
- **Büchel D**, Lehmann T & Baumeister J (2019). Effect of age on reactive multidirectional speed in highly trained young soccer players. Poster at the German Exercise Science & Training Conference in Würzburg. Germany.
- **Büchel D**, Döring M, Berkel F & Baumeister J (2019). Sports-specific differences in reactive multidirectional speed in team sports athletes using the Speedcourt. Poster at the German Exercise Science & Training Conference in Würzburg, Germany.
- Lehmann T, **Büchel D**, Cockcroft J, Louw Q & Baumeister J (2019). Phase Coupling of Bilateral Motor Areas Decreases From Bipedal to Single Leg Stance.

Poster at the 2019 Annual Meeting of the Organization of Human Brain Mapping in Rome, Italy.

- Lehmann T, Visser A, Havers T, **Büchel D** & Baumeister J (2022). Surface Instability Modulates Cortical Information Processing In Multi-Joint Compound Movements. Poster presentation at the Congress of the American College of Sports Medicine 2022 in San Diego, United States.
- **Büchel D**, Visser A, Lehmann T & Baumeister J (2022). Frontal theta power increases during table tennis play – indications for neurophysiological demands during open-skill sports ?. Poster at the 4th International Mobile Brain/Body Imaging Conference in San Diego, United States.

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